2-FLUOROBENZENESULFONYL COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

This invention is in the field of anti-inflammatory pharmaceutical agents and generally relates to compounds, compositions and methods for treating cyclooxygenase-2 mediated disorders, such as inflammation and inflammation-related disorders. The invention particularly relates to 2-fluorobenzenesulfonyl compounds, compositions and methods for treating cyclooxygenase-2 mediated disorders.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of antiinflammatory drug discovery. Common non-steroidal antiinflammatory drugs ("NSAIDs") that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are, however, also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

Recently, there has been significant research into some of the roles of cyclooxygenase-2. It has been found that COX-2 is upregulated in benign and malignant tumors (K. Subbaramaiah et al., Proc. Soc. Exp. Biol. Med., 216, 201 (1997)) including lung cancer (T. Hida et al., Anticancer Res., 18, 775-82 (1998)), Barrett's esophagus (K. Wilson,

Cancer Res., 58, 2929-34 (1998)) and skin cancer (S. Buckman et al., Carcinogenesis, 19, 723-29 (1998)). It is expressed in airway cells with implication in asthma (P. Barnes et al., Lung Biol. Health Dis., 114, 111-27 (1998)). Cox-2 also has a role in pre-term labor, angiogenesis (M. Tsujii et al. Cell, 93, 705-16 (1998)), vascular rejection (M. Bustos, J. Clin. Invest., 100, 1150-58 (1997)), HIV induced apoptosis (G. Bagetta et al., Biochem. Biophys. Res. Commun., 244, 819-24 (1998)), neurodegeneration (T. Sandhya et al., Brain Res., 788, 223-31 (1998)), inflammatory bowel disease, colitis, (I. Singer et al., Gastroenterology, 115, 297-306 (1998)), cerebral ischemia (S. Nogawa et al., Proc. Natl. Acad. Sci., 95, 10966-71 (1998)), and hypertension (A. Nasjletti, Hypertension, 31, 194-200 (1997)), among others.

Drugs that inhibit cyclooxygenase affect colon cancer (T. Kawamori et al., Cancer Res., 58, 409-12 (1998)), allergic neuritis (K. Miyamoto et al., Neuro Report, 9, 2331-4 (1998)), dementia, burn infections (M. Shoup, J. Trauma: Inj., Infec., Crit care, 45, 215-21 (1998)), cytomegalovirus infectivity (E. Speir et al., Circ. Res., 83, 210-16 (1998)), and lumbago (H. Bosch, Curr. Med. Res. Opin., 14, 29-38 (1997)), among others.

The references below disclose compounds having antiinflammatory activity and show that efforts are continuing to find a safe and effective antiinflammatory agent. WO96/19463 describes oxazoles substituted with a [(2- or 3)-halo-4-(alkylsulfonyl, aminosulfonyl or alkylaminosulfonyl)]phenyl group that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,380,738 describes 4-fluoro-phenyl and 4-methylsulfonyl substituted oxazoles that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,719,163 describes substituted oxazoles that selectively inhibit cyclooxygenase-2. WO96/36617 describes oxazoles that selectively inhibit cyclooxygenase-2. WO96/19462 describes oxazoles that selectively inhibit cyclooxygenase-2. WO98/11080 describes 3,4-diaryl-oxazolones that selectively inhibit cyclooxygenase-2.

EP 799,823 A1 describes 1- or 2-[3-halo-4-(methylsulfonyl, aminosulfonyl or substituted aminosulfonyl)phenyl]-pyrroles that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,935,990 describes substituted pyrroles that selectively inhibit cyclooxygenase-2.

WO99/64415 describes 1-(4-bromophenyl)-2-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methyl-1H-pyrrole; 5-(4-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-

(hydrogen, cyano, nitro, trifluoromethyl or ethoxycarbonyl)-1H-pyrazole; 2-[(4-bromophenyl) or (3-methyl-4-bromophenyl)]-1-[3-fluoro-4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole; 4-[2-(4-bromophenyl)-4-hydroxy-4-trifluoromethyl-1H-imidazol-1-yl]-2-fluorobenzene sulfonamide; 3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone; 3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl or aminosulfonyl)phenyl]-5-methylisoxazole; 4-(4-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl or aminosulfonyl)phenyl]-2-methyl-1,3-oxazole; and 4-(3-methyl-4-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-1,3-oxazole as intermediates used in the preparation of sulfonylbenzene compounds comprising an aryl or heteroaryl substituted phenyl moiety. WO99/64415 states that the disclosed sulfonylbenzene compounds are useful in the treatment of cyclooxygenase mediated diseases.

U.S. Patent No. 5,466,823, 5,504,215, 5,508,426, 5,510,496, 5,516,907, 5,521,207 and 5,760,068 describe substituted pyrazolyl benzenesulfonamides that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,475,018 describes 1,5-diphenyl pyrazoles that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,486,534 and 5,756,529 describe 3,4-substituted pyrazoles that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,401,765 and 5,639,777 describe 1,4,5-trisubstituted pyrazoles that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,434,178 and 5,908,852 describe 1,3,5-trisubstituted pyrazoles that selectively inhibit cyclooxygenase-2.

WO94/15932 describes thiophene and furan derivatives that selectively inhibit cyclooxygenase-2. WO94/26731 describes thiophene compounds that selectively inhibit cyclooxygenase-2. WO97/16435 describes 3,4-diaryl-2-hydroxy-2,5-dihydrofurans as prodrugs of compounds that are cyclooxygenase-2 inhibitors. GB 2,294,879 describes substituted furanones as cyclooxygenase-2 inhibitors.

U.S. Patent No. 5,859,257 describes substituted isooxazoles that selectively inhibit cyclooxygenase-2. EP 745596 describes substituted isooxazoles that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,344,991, 5,420,287 and 5,663,180 describe substituted cyclopentenes that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,418,254 describes substituted cyclopentadienyls that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,916,905 describes 2,3-substituted pyridines that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,596,008 describes 3,4-diaryl substituted pyridines that selectively inhibit cyclooxygenase-2. WO98/03484 describes substituted pyridines that selectively inhibit cyclooxygenase-2..

U.S. Patent No. 5,393,790 and 5,736,579 describe substituted spiro compounds that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,670,510, 5,672,626 and 5,672,627 describe spirodienes that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,668,161 describes substituted thiazoles that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,616,601 describes 1,2-substituted imidazoles that selectively inhibit cyclooxygenase-2. WO96/03387 describes 4,5-substituted imidazoles that selectively inhibit cyclooxygenase-2. WO96/03388 describes 1,2-substituted imidazoles that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,521,193 and 5,534,521 describe benzimidazoles that selectively inhibit cyclooxygenase-2.

WO94/13635 describes 5-methanesulfonamido-1-indanones that selectively inhibit cyclooxygenase-2. WO94/20480 describes alkanesulfonamido-1-indanones that selectively inhibit cyclooxygenase-2.

WO96/09293 describes benz[g]indazolyls that selectively inhibit cyclooxygenase-2.

WO98/47890 describes benzopyran derivatives that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,886,016 describes benzopyranopyrazolyls that selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,565,482 describes heteroarylpyranopyrazolyls that selectively inhibit cyclooxygenase-2.

U.S. Patent No. 5,739,166 describes substituted terphenyls that selectively inhibit cyclooxygenase-2.

Finally, various additional substituted sulfonamides have been described. Pyrazolyl-sulfonylureas have been described as having possible hypoglycemic activity [H. Faid-Allah and H. Mokhtar, Ind. J. Chem, 27, 245 (1988)]. JP

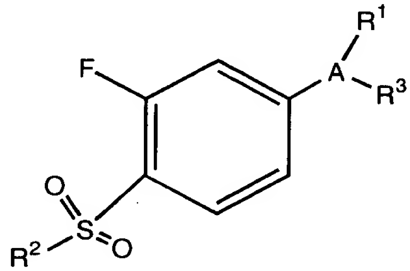
1,045,374 describes water soluble tetrazolium compounds useful in assays for determining reducing substances. D. Mukerjee et al [Acta. Pharma. Jugosl., 31, 151 (1981)] describe tetrazolium sulfonamides as antiviral agents. JP 4,277,724 describes triphenyl pyrazolines as nonlinear optical material. JP 5,323,522 describes the use of heterocyclic compounds in black and white photographic material. U.S. Patent No. 5,389,635 describes substituted imidazoles as angiotensin II antagonists. U.S. Patent No. 5,387,592 describes substituted benzimidazole derivatives as angiotensin II antagonists. G. Dorofeenko et al [Khim. Farm. Zh., 16, 920 (1982)] describe pyridinium salts as antiviral agents. U.S. Patent No. 5,338,749 describes diaryl-substituted heterocyclyl compounds as antiarthritis agents.

Compounds of the current invention, however, have not been described as antiinflammatory cyclooxygenase inhibitors.

DESCRIPTION OF THE INVENTION

The present invention comprises methods of treating cyclooxygenase-2 mediated disorders, such as inflammation, in a subject having or susceptible to such disorders by administering to the subject a therapeutically-effective amount of one or more compounds of Formulae I-VII as described below. The methods of the present invention also include prophylatic treatment of a subject. The compounds of Formulae I-VII comprise a class of 2-fluorobenzene sulfonyl compounds that are safe and effective anti-inflammatory agents. These compounds generally exhibit improved selectivity and/or potency in inhibiting cyclooxygenase-2 over cyclooxygenase-1 relative to the corresponding sulfonamides or methylsulfones lacking the orthofluoro substituent. The present invention further comprises those novel 2-fluorobenzene sulfonyl compounds within the class of compounds of Formulae I-VII.

More specifically, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from the class of compounds defined by Formula I:



I

wherein:

A is a 5- or 6-member ring substituent selected from partially saturated or unsaturated heterocyclic and carbocyclic rings;

R^1 is cyclohexyl, pyridinyl, or phenyl, wherein said cyclohexyl, pyridinyl, and phenyl may be optionally substituted with one, two or three radicals selected from C_{1-2}-alkyl, C_{1-2}-haloalkyl, cyano, carboxyl, C_{1-2}-alkoxycarbonyl, hydroxyl, C_{1-2}-hydroxyalkyl, C_{1-2}-haloalkoxy, amino, C_{1-2}-alkylamino, phenylamino, nitro, C_{1-2}-alkoxy-C_{1-2}-alkyl, C_{1-2}-alkylsulfinyl, halo, C_{1-2}-alkoxy and C_{1-3}-alkylthio;

R^2 is alkyl (particularly methyl) or amino; and

R^3 represents one or more radicals selected from hydrido, halo, C_{1-2}-alkyl, C_{2-3}-alkenyl, C_{2-3}-alkynyl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, heterocyclyloxy, C_{1-3}-alkoxy, C_{1-3}-alkylthio, alkylcarbonyl, cycloalkyl, phenyl, C_{1-3}-haloalkyl, heterocyclyl, cycloalkenyl, phenyl-C_{1-3}-alkyl, heterocyclyl-C_{1-3}-alkyl, C_{1-3}-alkylthio-C_{1-3}-alkyl, C_{1-3}-hydroxyalkyl, C_{1-3}-alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3}-alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl, N-phenylaminocarbonyl, N-(C_{1-3}-alkyl)-N-phenylaminocarbonyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3}-alkylamino, N-arylamino, N-aralkylamino, N-(C_{1-3}-alkyl)-N-aralkylamino, N-(C_{1-3}-alkyl)-N-arylamino, amino-C_{1-3}-alkyl, C_{1-3}-alkylaminoalkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylaminoalkyl, N-(C_{1-3}-alkyl)-N-(phenyl-C_{1-3}-alkyl)amino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenylalkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3}-alkylsulfinyl, C_{1-3}-alkylsulfonyl, aminosulfonyl, C_{1-3}-alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-(C_{1-3}-alkyl)-N-phenylaminosulfonyl;

or a pharmaceutically-acceptable salt, tautomer or prodrug thereof;

provided that, (a) A is not pyrrolyl, and (b) A is not oxazolyl other than oxazolonyl.

Within the above-described group of compounds, as well as for the compounds disclosed in the various embodiments of the invention set forth throughout the instant application, one or more of the following conditions preferably is satisfied:

(1) when R^1 is 4-bromophenyl: (a) A is not pyrazolyl when R^2 is methyl and R^3 is hydrogen, cyano, trifluoromethyl or ethoxycarbonyl; (b) A is not imidazolyl when R^3 is trifluoromethyl; (c) A is not isoxazolyl when R^3 is methyl; and (d) A is not 2-furanonyl when R^3 is hydrogen;

(2) when R^1 is 3-methyl-4-bromophenyl, R^2 is methyl and R^3 is trifluoromethyl, A is not imidazolyl;

(3) R^1 is other than 4-bromophenyl;

(4) R^1 is other than 4-bromophenyl or 3-methyl-4-bromophenyl; and/or

(5) R^1 is other than bromophenyl.

In another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a preferred class of compounds consisting of those compounds of Formula I wherein:

A is a 5- or 6-member ring substituent selected from partially saturated or unsaturated heterocyclic and carbocyclic rings;

R^1 is cyclohexyl, pyridinyl, or phenyl, wherein said cyclohexyl, pyridinyl, and phenyl may be optionally substituted with one, two or three radicals selected from C_{1-2}-alkyl, C_{1-2}-haloalkyl, cyano, carboxyl, C_{1-2}-alkoxycarbonyl, hydroxyl, C_{1-2}-hydroxyalkyl, C_{1-2}-haloalkoxy, amino, C_{1-2}-alkylamino, phenylamino, nitro, C_{1-2}-alkoxy-C_{1-2}-alkyl, C_{1-2}-alkylsulfinyl, halo, C_{1-2}-alkoxy and C_{1-3}-alkylthio;

R^2 is methyl or amino; and

R^3 represents one or more radicals selected from hydrido, halo, C_{1-2}-alkyl, C_{2-3}-alkenyl, C_{2-3}-alkynyl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, (5- or 6- member ring heterocyclyl)oxy, C_{1-3}-alkoxy, C_{1-3}-alkylthio, C_{1-3}-alkylcarbonyl, C_{3-6}-cycloalkyl, phenyl, C_{1-3}-haloalkyl, 5- or 6- member ring heterocyclyl, C_{3-6}-cycloalkenyl, phenyl-C_{1-3}-alkyl, (5- or 6-member ring heterocyclyl)-C_{1-3}-alkyl, C_{1-3}-alkylthio-C_{1-3}-alkyl, C_{1-3}-hydroxyalkyl, C_{1-3}-

alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3}-alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenyloxy-C_{1-3}-alkyl, C_{1-3}-alkoxyphenyl-C_{1-3}-alkoxy-C_{1-3}-alkyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl, N-phenylaminocarbonyl, N-(C_{1-3}-alkyl)-N-phenylaminocarbonyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3}-alkylamino, N-phenylamino, N-(phenyl-C_{1-3}-alkyl)amino, N-(C_{1-3}-alkyl)-N-(phenyl-C_{1-3}-alkyl)amino, N-(C_{1-3}-alkyl)-N-phenylamino, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenyl-C_{1-3}-alkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3}-alkylsulfinyl, C_{1-3}-alkylsulfonyl, aminosulfonyl, C_{1-3}-alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-(C_{1-3}-alkyl)-N-phenylaminosulfonyl;

or a pharmaceutically-acceptable salt, tautomer or prodrug thereof.

Within this preferred class of compounds, A preferably is a radical selected from thienyl, furyl, furanone, thiazolyl, oxothiazolyl, thioxothiazolyl, imidazolyl, benzofuryl, indenyl, benzothienyl, isoxazolyl, oxooxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, benzopyranopyrazolyl, phenyl, and pyridyl. More preferably, A is a radical selected from thienyl, furyl, furanone, thiazolyl, oxothiazolyl, thioxothiazolyl, imidazolyl, benzofuryl, indenyl, benzothienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, benzopyranopyrazolyl, phenyl, and pyridyl. Still more preferably, A is a radical selected from thienyl, furanone, isoxazolyl, pyrazolyl, cyclopentenyl and pyridinyl. Still more preferably, A is a radical selected from furanone, isoxazolyl, and pyrazolyl.

In another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a more preferred class of compounds consisting of compounds of Formula I wherein one or both of R^1 and R^3 are defined as follows:

R^1 is cyclohexyl, pyridinyl, or phenyl, wherein said cyclohexyl, pyridinyl, and phenyl may be optionally substituted with one, two or three radicals selected from methyl,

difluoromethyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, hydroxyl, hydroxymethyl, trifluoromethoxy, amino, methylamino, phenylamino, nitro, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy and methylthio; and/or

R^3 is a radical selected from hydrido, fluoro, chloro, bromo, methyl, oxo, cyano, carboxyl, cyanomethyl, methoxy, methylthio, methylcarbonyl, phenyl, trifluoromethyl, difluoromethyl, phenylmethyl, methylthiomethyl, hydroxymethyl, methoxycarbonyl, ethoxycarbonyl, phenylcarbonyl, phenylmethylcarbonyl, methoxymethyl, phenylthiomethyl, phenyloxymethyl, methoxyphenylmethoxymethyl, methoxycarbonylmethyl, aminocarbonyl, aminocarbonylmethyl, methylaminocarbonyl, N-phenylaminocarbonyl, N-methyl-N-phenylaminocarbonyl, methylaminocarbonylmethyl, carboxymethyl, methylamino, N-phenylamino, N-(phenylmethyl)amino, N-methyl-N-(phenylmethyl)amino, N-methyl-N-phenylamino, aminomethyl, methylaminomethyl, N-phenylaminomethyl, N-phenylmethylaminomethyl, N-methyl-N-phenylmethylaminomethyl, N-methyl-N-phenylaminomethyl, phenyloxy, phenylmethoxy, phenylthio, phenylmethylthio, methylsulfinyl, methylsulfonyl, aminosulfonyl, methylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-methyl-N-phenylaminosulfonyl.

In another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a still more preferred class of compounds consisting of those compounds of Formula I wherein:

R^1 is cyclohexyl or phenyl, wherein said cyclohexyl and phenyl may be optionally substituted with one, two or three radicals selected from halo, cyano, C_{1-2}-alkyl, C_{1-2}-haloalkyl, C_{1-2}-alkoxy, and C_{1-2}-haloalkoxy; and

R^3 is a radical selected from hydrido, C_{1-2}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylcarbonyl, C_{1-3}-haloalkyl, and C_{1-3}-alkoxycarbonyl.

In another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a still more preferred group of compounds consisting of those compounds of Formula I wherein:

R^1 is cyclohexyl or phenyl, wherein said cyclohexyl and phenyl may be optionally substituted with one, two or three radicals selected from methyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, cyano, fluoro, chloro, bromo, and methoxy; and

R^3 is a radical selected from hydrido, methyl, methoxy, methylcarbonyl, trifluoromethyl, difluoromethyl, and methoxycarbonyl.

In another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from the group consisting of those compounds having a structure identical to compounds of Formula I except that the fluoro radical is in the meta position of the phenyl ring relative to the sulfonyl group rather than in the ortho position.

Utility of Methods and Compounds

The methods and compounds of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other cyclooxygenase-2 mediated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, the methods and compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such methods and compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery.

The methods and compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

The methods and compounds of the invention would be useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

The methods and compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

The methods and compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as associated with osteoporosis.

The methods and compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" includes partial or total inhibition of the dementia, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, and senile dementia.

The methods and compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These methods and compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and liver disease. The methods and compounds would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

The methods and compounds above would be useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. The methods and compounds would be useful for treatment and prevention of vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including

cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

The methods and compounds would be useful for, but not limited to, the treatment of angiogenesis-related disorders in a subject. According to the present invention, the methods and compounds can be used in the treatment of a subject in need of angiogenesis inhibition. The methods and compounds would be useful for treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

The methods and compounds of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The methods and compounds can also be used to treat the fibrosis which occurs with radiation therapy. The methods and compounds can be used to treat subjects having adenomatous

polyps, including those with familial adenomatous polyposis (FAP). Additionally, the methods and compounds can be used to prevent polyps from forming in patients at risk of FAP.

The methods and compounds of the present invention may be used alone or in conjunction with additional therapies and/or compounds known to those skilled in the art in the prevention or treatment of neoplasia. Alternatively, the methods and compounds described herein may be used in conjunctive therapy. By way of example, the compounds may be administered alone or in conjunction with other antineoplastic agents or other growth inhibiting agents or other drugs or nutrients.

The present methods and compounds may also be used in co-therapies, partially or completely, in addition to other antiinflammatories, such as together with steroids, NSAIDs, iNOS inhibitors, p38 inhibitors, MMP inhibitors, TNF inhibitors, 5-lipoxygenase inhibitors, LTB4 receptor antagonists and LTA4 hydrolase inhibitors.

The present methods and compounds may also be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. More preferred would be combinations with compounds selected from morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, Tramadol [(+) enantiomer], DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetominophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirfentanil, amitriptyline, DuP631, Tramadol [(-) enantiomer], GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, Dynorphine A, E-2078, AXC3742, SNX-111, ADL2-1294, ICI-204448, CT-3, CP-99,994, and CP-99,994.

The methods and compounds can be used in co-therapies, in place of other conventional antiinflammatories, in combination with one or more antihistamines, decongestants, diuretics, antitussive agents or with other agents previously known to be effective in combination with antiinflammatory agents.

Subjects of Treatment

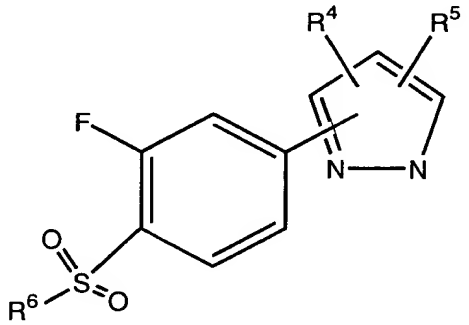
Besides being useful for human treatment, these methods and compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

Selectivity of Compounds

The present novel methods preferably employ compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 5 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Pyrazoles

In still another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a subclass of compounds of Formula I corresponding to Formula II:

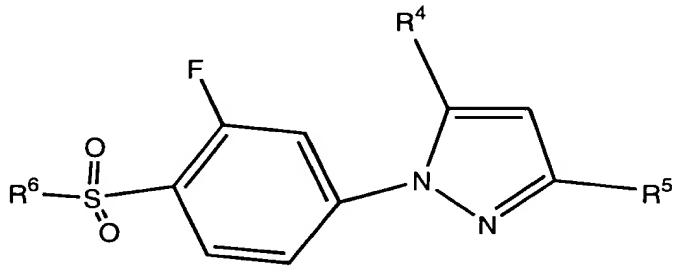


II

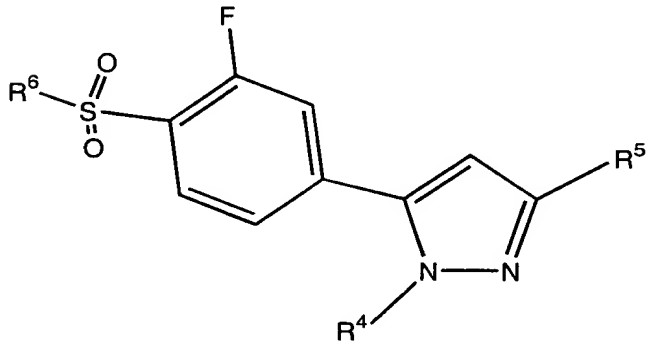
wherein substituents R^4, R^5 and R^6 have the same definitions and sub-definitions as substituents R^1, R^3 and R^2, respectively, set forth above for the compounds of Formula I, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. Preferably, R^4 is

not 4-bromophenyl when R^6 is methyl and R^5 is hydrogen, cyano, trifluoromethyl or ethoxycarbonyl.

Within this subclass of compounds, a preferred group of compounds consists of those compounds of Formula IIA or Formula IIB:



IIA



IIB

wherein R^4, R^5 and R^6 are as defined above, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Preferred species within this subclass include, but are not limited to:

5-phenyl-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-chlorophenyl)-1-[3-fluoro-4(methylsulfonyl)phenyl] -3-(trifluoromethyl)-1H-pyrazole;

5-(4-chlorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]- 3-(trifluoromethyl)-1H-pyrazole;

5-(3-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]- 3-(trifluoromethyl)-1H-pyrazole;

5-(4-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-cyanophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-cyanophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,4-dichlorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,4-dibromophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]- 3-(trifluoromethyl)-1H-pyrazole;

5-(3,4-difluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,5-dichlorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,5-dibromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,5-difluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,4-dimethylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3,5-dimethylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-methyl-4-chlorophenyl)-1-[3-fluoro-4 (methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-methyl-3-chlorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-methyl-4-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-methyl-3-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-methyl-4-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-methyl-3-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-methyl-4-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-methyl-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-methyl-4-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-methyl-3-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-cyano-4-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-cyano-3-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-chloro-4-methoxyphenyl)-1-[3-fluoro-4(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-chloro-3-methoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-6-yl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(2-methylthiazol-4-yl)-1-[3-fluoro-4 (methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(4-methylthiazol-2-yl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-3-yl)-1-[3-fluoro-4 (methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-3-yl)-1-[3-fluoro(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(3-pyridinyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(5-methylpyridin-3-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-3-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-cyclohexyl-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-cyclopentyl-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

5-phenyl-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-chlorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3(difluoromethyl)-1H-pyrazole;

5-(4-chlorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-cyanophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-cyanophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,4-dichlorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,4-dibromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]- 3-(difluoromethyl)-1H-pyrazole;

5-(3,4-difluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,5-dichlorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,5-dibromophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,5-difluorophenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,4-dimethylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3,5-dimethylphenyl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-methyl-4-chlorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methyl-3-chlorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-methyl-4-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methyl-3-fluorophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-methyl-4-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methyl-3-bromophenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-methyl-4-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methyl-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-methyl-4-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methyl-3-trifluoromethoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-cyano-4-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-cyano-3-methylphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-chloro-4-methoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-chloro-3-methoxyphenyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-6-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(2-methylthiazol-4-yl)-1-[3-fluoro-4(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(4-methylthiazol-2-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-3-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-3-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(3-pyridinyl)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(5-methylpyridin-3-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-(2-methylpyridin-3-yl)-1-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-cyclohexyl-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

5-cyclopentyl-1-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-phenyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]- 3-(trifluoromethyl)-1H-pyrazole;

1-(4-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-cyanophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-cyanophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,4-dichlorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,4-dibromophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]- 3-(trifluoromethyl)-1H-pyrazole;

1-(3,4-difluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,5-dichlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,5-dibromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,5-difluorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,4-dimethylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3,5-dimethylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-methyl-4-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-methyl-3-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-methyl-4-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-methyl-3-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-methyl-4-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-methyl-3-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-methyl-4-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-methyl-3-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-methyl-4-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-methyl-3-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-cyano-4-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-cyano-3-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-chloro-4-methoxyphenyl)-5-[3-fluoro-4(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-chloro-3-methoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-6-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(2-methylthiazol-4-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(4-methylthiazol-2-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(3-pyridinyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(5-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-cyclohexyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-cyclopentyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

1-phenyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-cyanophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-cyanophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,4-dichlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,4-dibromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,4-difluorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,5-dichlorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,5-dibromophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,5-difluorophenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,4-dimethylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3,5-dimethylphenyl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-methyl-4-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methyl-3-chlorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-methyl-4-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methyl-3-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-methyl-4-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methyl-3-bromophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-methyl-4-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methyl-3-trifluoromethylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-methyl-4-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methyl-3-trifluoromethoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-cyano-4-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-cyano-3-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-chloro-4-methoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-chloro-3-methoxyphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-6-yl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(2-methylthiazol-4-yl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(4-methylthiazol-2-yl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(3-pyridinyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(5-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-(2-methylpyridin-3-yl)-5-[3-fluoro-4-(methylsulfonyl) phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-cyclohexyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

1-cyclopentyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

2-fluoro-4-[1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-bromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-bromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-cyanophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-cyanophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-trifluoromethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-trifluoromethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-trifluoromethoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-trifluoromethoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,4-dichlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,4-dibromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide

2-fluoro-4-[1-(3,4-difluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-dichlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-dibromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-difluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,4-dimethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-dimethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-bromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-bromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-trifluoromethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-trifluoromethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-trifluoromethoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-trifluoromethoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-cyano-4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-cyano-3-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-chloro-3-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-6-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylthiazol-4-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methylthiazol-2-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-3-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-3-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-pyridinyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(5-methylpyridin-3-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-3-yl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-cyclohexyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-cyclopentyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,4-dibromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide

2-fluoro-4-[1-(3,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-dibromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,4-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3,5-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-methyl-4-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methyl-3-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-cyano-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-cyano-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-chloro-3-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-6-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylthiazol-4-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(4-methylthiazol-2-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(5-methylpyridin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-(2-methylpyridin-3-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

2-fluoro-4-[1-cyclohexyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

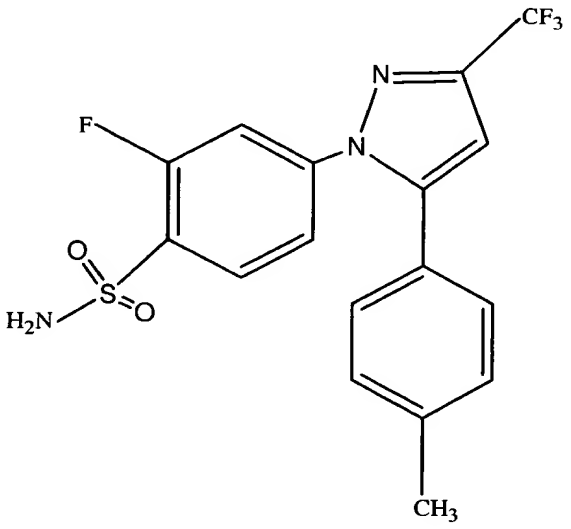
2-fluoro-4-[1-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benezenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide;

4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-1-yl]-2-fluorobenzenesulfonamide;

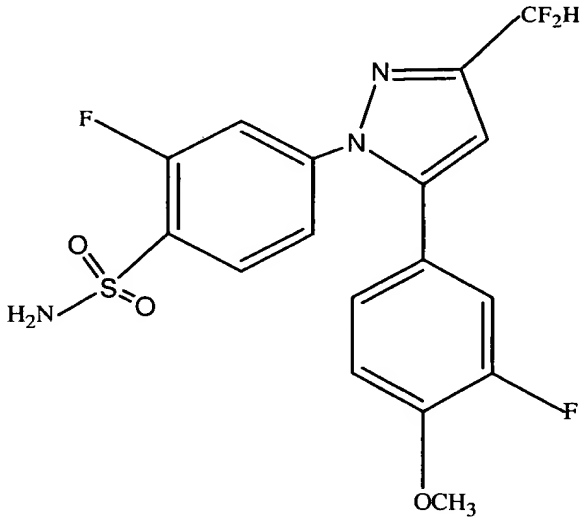
and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

In one embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

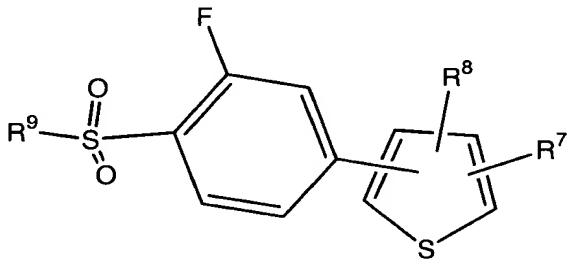
In another embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

Thiophenes

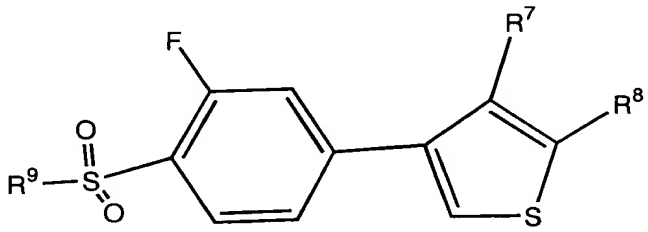
In still another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a subclass of compounds of Formula I corresponding to Formula III:



III

wherein substituents R^7, R^8 and R^9 have the same definitions and sub-definitions as substituents R^1, R^3 and R^2, respectively, set forth above for the compounds of Formula I, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Within this subclass of compounds, a preferred group of compounds consists of those compounds of Formula IIIA:



IIIA

wherein R^7, R^8 and R^9 are as defined above, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Within this subclass of compounds, another preferred group of compounds, in addition to those embodiments previously described with respect to compounds of Formula I, consists of those compounds of Formula III wherein:

R^7 is cyclohexyl or phenyl, wherein said cyclohexyl and phenyl may be optionally substituted with one, two or three radicals selected from halo, cyano, C_{1-2}-alkyl, C_{1-2}-haloalkyl, C_{1-2}-alkoxy, and C_{1-2}-haloalkoxy; and

R^8 is a radical selected from hydrido, halogen, C_{1-2}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkylcarbonyl, C_{1-3}-haloalkyl, and C_{1-3}-alkoxycarbonyl.

Within this subclass of compounds, another preferred group of compounds, in addition to those embodiments previously described with respect to compounds of Formula I, consists of those compounds of Formula III wherein:

R^7 is cyclohexyl or phenyl, wherein said cyclohexyl and phenyl may be optionally substituted with one, two or three radicals selected from methyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, cyano, fluoro, chloro, bromo, and methoxy; and

R^8 is a radical selected from hydrido, chloro, fluoro, bromo, iodo, cyano, methyl, methoxy, methylcarbonyl, trifluoromethyl, difluoromethyl, and methoxycarbonyl.

Preferred species within this subclass include, but are not limited to:

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;
3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl] thiophene;
3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;
3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;
3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;
3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;
3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;
3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;
3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;
3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;
3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;
3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;
3-(4-trifluoromethylphenyl)-4-[3-fluoro-4 (methylsulfonyl)phenyl]thiophene;
3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;
3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-thiophene;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-thiophene;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-thiophene;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-thiophene;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]thiophene;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]thiophene;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl) phenyl] thiophene;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl) phenyl] thiophene;

2-fluoro-4-[4-phenyl-3-thiophenyl]benezenesulfonamide;

2-fluoro-4-[4-(3-chlorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-chlorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-bromophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-bromophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-fluorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-fluorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-methylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-methylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-cyanophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-cyanophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-trifluoromethylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-trifluoromethylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-trifluoromethoxyphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-trifluoromethoxyphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,4-dichlorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,4-dibromophenyl)-3-thiophenyl] benezenesulfonamide

2-fluoro-4-[4-(3,4-difluorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,5-dichlorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,5-dibromophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,5-difluorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,4-dimethylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3,5-dimethylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-methyl-4-chlorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-methyl-3-chlorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-methyl-4-fluorophenyl)-3-thiophenyl]benezenesulfonamide;

2-fluoro-4-[4-(4-methyl-3-fluorophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-methyl-4-bromophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-methyl-3-bromophenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-methyl-4-trifluoromethylphenyl)-3-thiophenyl]benezene-sulfonamide;

2-fluoro-4-[4-(4-methyl-3-trifluoromethylphenyl)-3-thiophenyl]benezene-sulfonamide;

2-fluoro-4-[4-(3-methyl-4-trifluoromethoxyphenyl)-3-thiophenyl]benezene-sulfonamide;

2-fluoro-4-[4-(4-methyl-3-trifluoromethoxyphenyl)-3-thiophenyl]benezene-sulfonamide;

2-fluoro-4-[4-(3-cyano-4-methylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-cyano-3-methylphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-chloro-4-methoxyphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-chloro-3-methoxyphenyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(2-methylpyridin-6-yl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(2-methylthiazol-4-yl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(4-methylthiazol-2-yl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(2-methylpyridin-3-yl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(2-methylpyridin-3-yl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(3-pyridinyl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(5-methylpyridin-3-yl)-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-(2-methylpyridin-3-yl)-3-thiophenyl] benezenesulfonamide;

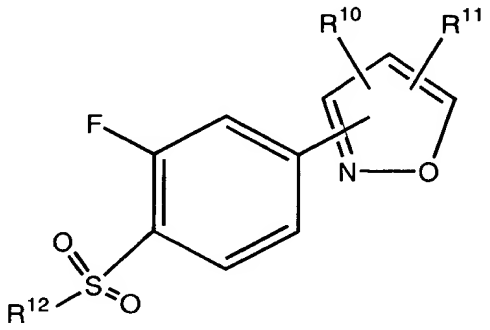
2-fluoro-4-[4-cyclohexyl-3-thiophenyl] benezenesulfonamide;

2-fluoro-4-[4-cyclopentyl-3-thiophenyl] benezenesulfonamide;

and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Isoxazoles

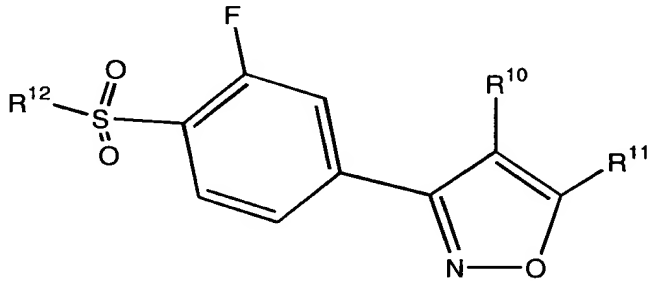
In still another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a subclass of compounds of Formula I corresponding to Formula IV:



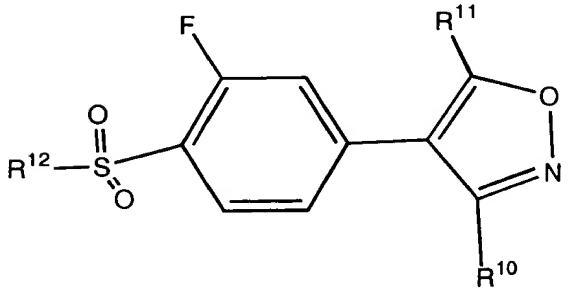
IV

wherein substituents R^{10}, R^{11} and R^{12} have the same definitions and sub-definitions as substituents R^1, R^3 and R^2, respectively, set forth above for the compounds of Formula I, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. Preferably, R^{10} is not 4-bromophenyl when R^{11} is methyl.

Within this subclass of compounds, a preferred group of compounds consists of those compounds of Formula IVA and IVB:



IVA



IVB

wherein R^{10}, R^{11} and R^{12} are as defined above, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Preferred species within this subclass include, but are not limited to:

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethyl-isoxazole;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-trifluoromethylisoxazole;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-trifluoromethylisoxazole;

2-fluoro-4-[3-phenyl-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methylphenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-5-fluoromethyl-soxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide

2-fluoro-4-[3-(3,4-difluorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-5-fluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-fluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-cyclohexyl-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-cyclopentyl-5-fluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-phenyl-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-5-difluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-5-difluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-5-difluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-5-difluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-5-difluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-5-difluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-5-difluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methylphenyl)-5-difluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-5-difluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-5-difluoromethylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-5-difluoro-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-5-difluoro-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-difluorophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

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2-fluoro-4-[3-(4-methyl-3-bromophenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-difluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-cyclohexyl-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-cyclopentyl-5-difluoromethylisoxazol-4-yl]benezenesulfonamide;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-hydroxymethylisoxazole;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-hydroxymethylisoxazole;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]- 5-fluoromethylisoxazole;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-fluoromethylisoxazole;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-fluoromethylisoxazole;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-difluoromethylisoxazole;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-difluoromethylisoxazole;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-methylsulfonyl) phenyl]-5-methylisoxazole;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-5-methylisoxazole;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-5-methylisoxazole;

2-fluoro-4-[3-phenyl-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methylphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide

2-fluoro-4-[3-(3,4-difluorophenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-5-hydroxy-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-hydroxymethy-lisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-hydroxymethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-cyclohexyl-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-cyclopentyl-5-hydroxymethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-phenyl-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide

2-fluoro-4-[3-(3,4-difluorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-5-methylisoxazol -4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-5-methylisoxazol -4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-5-methyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-5-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-5-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-5-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-methylisoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-cyclohexyl-5-methylisoxazol-4-yl] benezenesulfonamide;

2-fluoro-4-[3-cyclopentyl-5-methylisoxazol-4-yl] benezenesulfonamide;

2-fluoro-4-[3-phenyl-5-trifluoromethylisoxazol-4-yl] benezenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-5 trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-methylphenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezene-sulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide

2-fluoro-4-[3-(3,4-difluorophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-5-trifluoro-methylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-5-trifluoromethyl-isoxazol-4-yl]benezenesulfonamide;

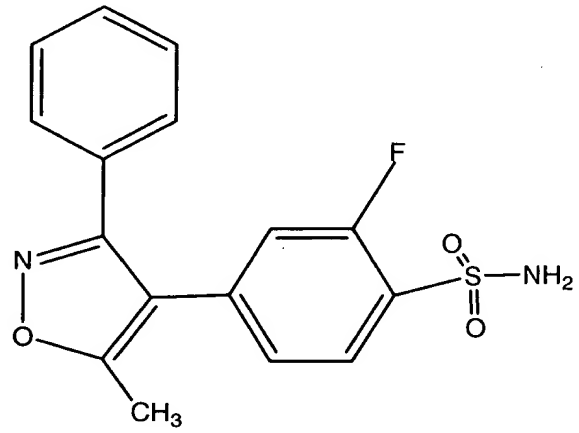
2-fluoro-4-[3-cyclohexyl-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-cyclopentyl-5-trifluoromethylisoxazol-4-yl]benezenesulfonamide;

2-fluoro-4-[3-phenyl-5-methyl-4-isoxazolyl]-benzenesulfonamide;

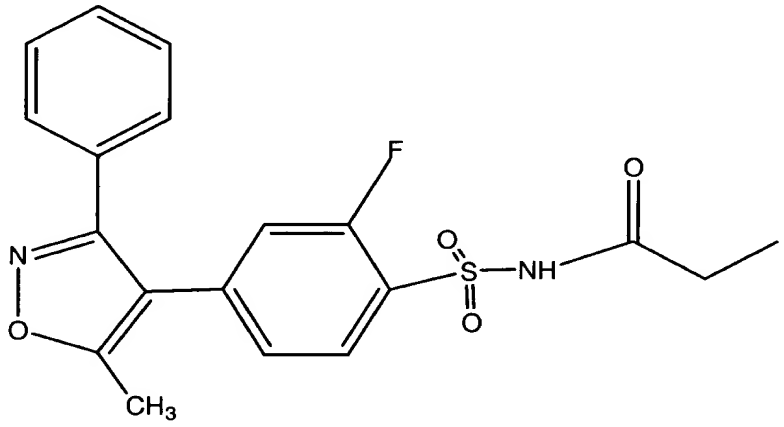
and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

In one embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

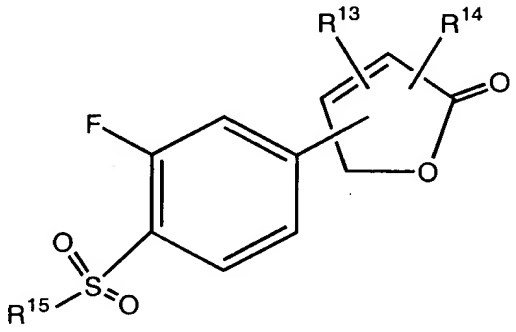
In another embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

Furanones

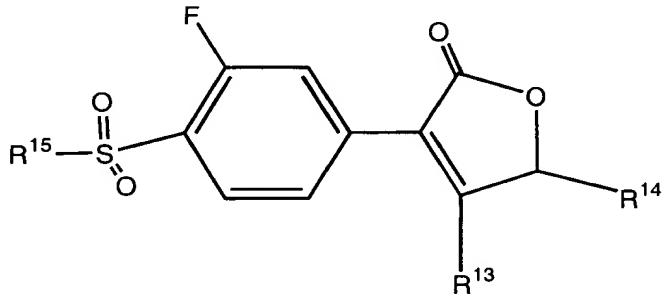
In still another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a subclass of compounds of Formula I corresponding to Formula V:



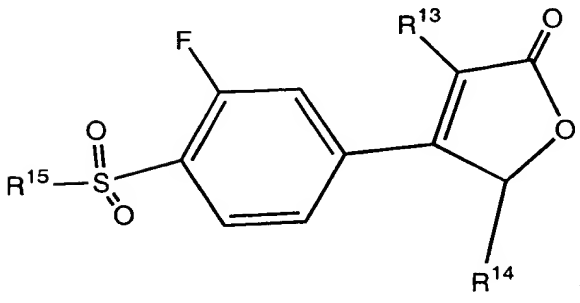
V

wherein substituents R^{13}, R^{14} and R^{15} have the same definitions and sub-definitions as substituents R^1, R^3 and R^2, respectively, set forth above for the compounds of Formula I, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. Preferably, R^{13} is not 4-bromophenyl when R^{14} is hydrogen.

Within this subclass of compounds, a preferred group of compounds consists of those compounds of Formula VA and VB:



VA



VB

wherein R^{13}, R^{14} and R^{15} are as defined above, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Preferred species within this subclass include, but are not limited to:

2-fluoro-4-[4-5-oxo-2,5-dihydro-3-furanyl] benzenesulfonamide;

2-fluoro-4-[4-(3-chlorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-chlorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-bromophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-bromophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-fluorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-fluorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-methylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-methylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-cyanophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-cyanophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-trifluoromethylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-trifluoromethylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-trifluoromethoxyphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-trifluoromethoxyphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3,4-dichlorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3,4-dibromophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide

2-fluoro-4-[4-(3,4-difluorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3,5-dichlorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3,5-dibromophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3,5-difluorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3,4-dimethylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3,5-dimethylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-methyl-4-chlorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-methyl-3-chlorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-methyl-4-fluorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-methyl-3-fluorophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-methyl-4-bromophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-methyl-3-bromophenyl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-methyl-4-trifluoromethylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-methyl-3-trifluoromethylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-methyl-4-trifluoromethoxyphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-methyl-3-trifluoromethoxyphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-cyano-4-methylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-cyano-3-methylphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(3-chloro-4-methoxyphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(4-chloro-3-methoxyphenyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(2-methylpyridin-6-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(2-methylthiazol-4-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(4-methylthiazol-2-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(2-methylpyridin-3-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(2-methylpyridin-3-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(3-pyridinyl)-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-(5-methylpyridin-3-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-(2-methylpyridin-3-yl)-5-oxo-2,5-dihydro-3-furanyl]benzene-sulfonamide;

2-fluoro-4-[4-cyclohexyl-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

2-fluoro-4-[4-cyclopentyl-5-oxo-2,5-dihydro-3-furanyl]benzenesulfonamide;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] -2(5H)-furanone;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] -2(5H)-furanone;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2(5H)-furanone;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2(5H)-furanone;

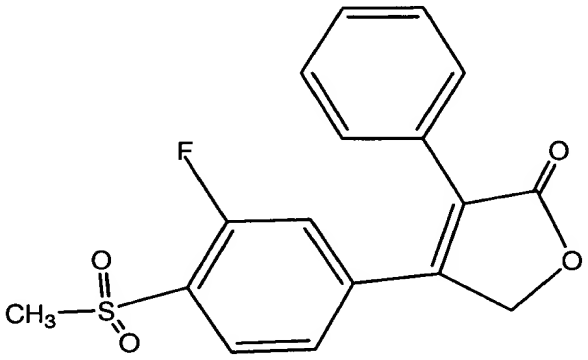
3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2(5H)-furanone;

4-[3-fluoro-4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

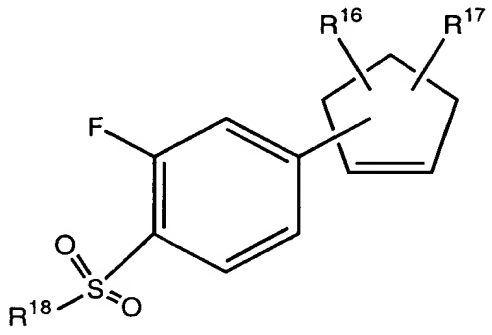
In one embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

Cyclopentenes

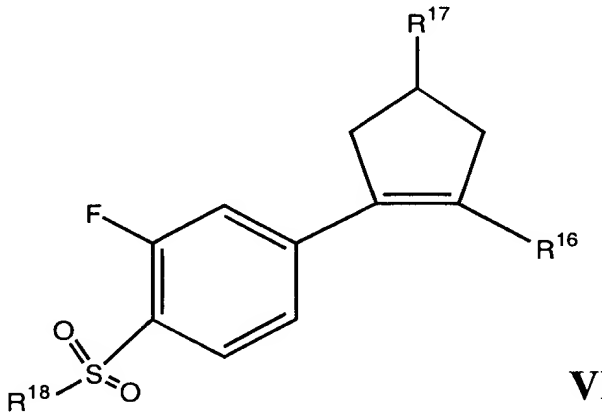
In still another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective amount of one or more compounds selected from a subclass of compounds of Formula I corresponding to Formula VI:



VI

wherein substituents R^{16}, R^{17} and R^{18} have the same definitions and sub-definitions as substituents R^1, R^3 and R^2, respectively, set forth above for the compounds of Formula I, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Within this subclass of compounds, a preferred group of compounds consists of those compounds of Formula VIA:



VIA

wherein R^{16}, R^{17} and R^{18} are as defined above, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Preferred species within this subclass include, but are not limited to:

2-fluoro-4-[2-phenylcyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-chlorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(4-chlorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-bromophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(4-bromophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-fluorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(4-fluorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-methylphenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(4-methylphenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-cyanophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(4-cyanophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-trifluoromethylphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-trifluoromethoxyphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-trifluoromethoxyphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3,4-dichlorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,4-dibromophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,4-difluorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,5-dichlorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,5-dibromophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,5-difluorophenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,4-dimethylphenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3,5-dimethylphenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-methyl-4-chlorophenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-methyl-3-chlorophenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-methyl-4-fluorophenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-methyl-3-fluorophenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-methyl-4-bromophenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-methyl-3-bromophenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-methyl-4-trifluoromethylphenyl) cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-methyl-3-trifluoromethylphenyl) cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-methyl-4-trifluoromethoxyphenyl) cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-methyl-3-trifluoromethoxyphenyl) cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-cyano-4-methylphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-cyano-3-methylphenyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-chloro-3-methoxyphenyl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(2-methylpyridin-6-yl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(2-methylthiazol-4-yl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(4-methylthiazol-2-yl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(2-methylpyridin-3-yl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(2-methylpyridin-3-yl)cyclopenten-1-yl]benezenesulfonamide;

2-fluoro-4-[2-(3-pyridinyl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(5-methylpyridin-3-yl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-(2-methylpyridin-3-yl)cyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-cyclohexylcyclopenten-1-yl] benezenesulfonamide;

2-fluoro-4-[2-cyclopentylcyclopenten-1-yl] benezenesulfonamide;

4-[2-phenylcyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-chlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-chlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-bromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-bromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-fluorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-fluorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-cyanophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-cyanophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-trifluoromethylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-trifluoromethoxyphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-trifluoromethoxyphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,4-dichlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,4-dibromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,4-difluorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,5-dichlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,5-dibromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,5-difluorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,4-dimethylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3,5-dimethylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methyl-4-chlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methyl-3-chlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methyl-4-fluorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methyl-3-fluorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methyl-4-bromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methyl-3-bromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methyl-4-trifluoromethylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methyl-3-trifluoromethylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methyl-4-trifluoromethoxyphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methyl-3-trifluoromethoxyphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-cyano-4-methylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-cyano-3-methylphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-chloro-3-methoxyphenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(2-methylpyridin-6-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(2-methylthiazol-4-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(4-methylthiazol-2-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(2-methylpyridin-3-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(2-methylpyridin-3-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-pyridinyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(5-methylpyridin-3-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(2-methylpyridin-3-yl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

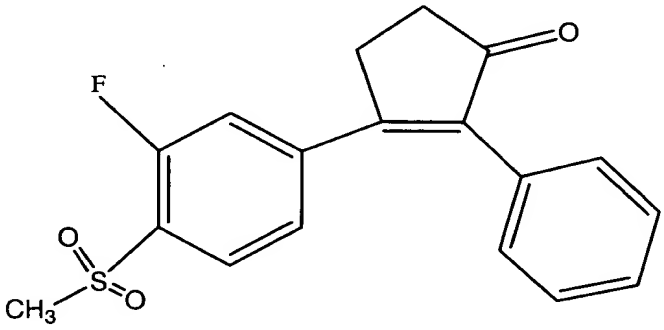
4-[2-cyclohexylcyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-cyclopentylcyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

2-(3,5-difluorophenyl)-3-(3-fluoro-4-(methylsulfonyl)phenyl))-2-cyclopenten-1-one;

and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

In one embodiment, the species is:

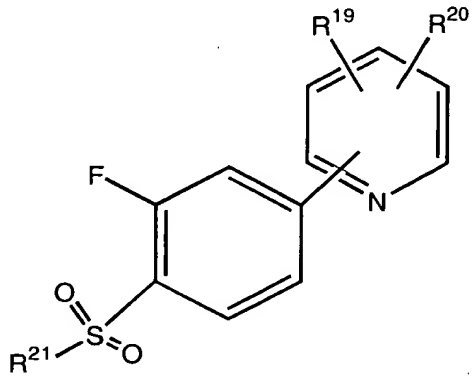


and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

Pyridines

In still another embodiment, the present method of treating cyclooxygenase-2 mediated disorders comprises administering to the subject a therapeutically-effective

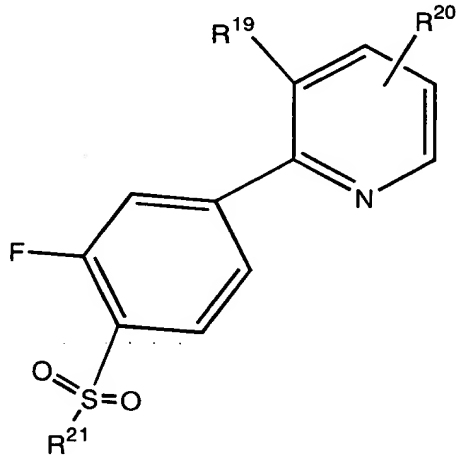
amount of one or more compounds selected from a subclass of compounds of Formula I corresponding to Formula VII:



VII

wherein substituents R^{19}, R^{20} and R^{21} have the same definitions and sub-definitions as substituents R^1, R^3 and R^2, respectively, set forth above for the compounds of Formula I, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Within this subclass of compounds, a preferred group of compounds consists of those compounds of Formula VIIA:



VIIA

wherein R^{19}, R^{20} and R^{21} are as defined above, and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Preferred species within this subclass include, but are not limited to:

2-fluoro-4-[3-phenyl-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3-chlorophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(4-chlorophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(3-bromophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(4-bromophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(3-fluorophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(4-fluorophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(3-methylphenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(4-methylphenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(3-cyanophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(4-cyanophenyl)-3-pyridinyl]-benezene-sulfonamide;
2-fluoro-4-[3-(3-trifluoromethylphenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(4-trifluoromethylphenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,4-dichlorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,4-dibromophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,4-difluorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,5-dichlorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,5-dibromophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,5-difluorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,4-dimethylphenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3,5-dimethylphenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(3-methyl-4-bromophenyl)-3-pyridinyl]-benezenesulfonamide;
2-fluoro-4-[3-(4-methyl-3-bromophenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-3-pyridinyl]-benezene-sulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-3-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-cyclohexyl-3-pyridinyl]-benezene-sulfonamide;

2-fluoro-4-[3-cyclopentyl-3-pyridinyl]-benezene-sulfonamide;

2-fluoro-4-[3-phenyl-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-2-pyridinyl]-benezene-sulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,4-difluorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-cyclohexyl-2-pyridinyl]-benezenesulfonamide;

2-fluoro-4-[3-cyclopentyl-2-pyridinyl]-benezenesulfonamide;

4-[3-phenyl-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-chlorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-chlorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-bromophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-bromophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-fluorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-fluorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-methylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-cyanophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-cyanophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-trifluoromethylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-trifluoromethylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-trifluoromethoxyphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-trifluoromethoxyphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,4-dichlorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,4-dibromophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,4-difluorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,5-dichlorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,5-dibromophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,5-difluorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,4-dimethylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3,5-dimethylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-methyl-4-chlorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methyl-3-chlorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-methyl-4-fluorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methyl-3-fluorophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-methyl-4-bromophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methyl-3-bromophenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-methyl-4-trifluoromethylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methyl-3-trifluoromethylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-methyl-4-trifluoromethoxyphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methyl-3-trifluoromethoxyphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-cyano-4-methylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-cyano-3-methylphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-chloro-4-methoxyphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-chloro-3-methoxyphenyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(2-methylpyridin-6-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(2-methylthiazol-4-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(4-methylthiazol-2-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(2-methylpyridin-3-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(2-methylpyridin-3-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(3-pyridinyl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(5-methylpyridin-3-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-(2-methylpyridin-3-yl)-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-cyclohexyl-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[3-cyclopentyl-2-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-phenyl-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-chlorophenyl)-3-pyridinyl]-2-fluorophenyl methyl ulfone;

4-[4-(4-chlorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-bromophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-bromophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-fluorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-fluorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-methylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-cyanophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-cyanophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-trifluoromethylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-trifluoromethylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-trifluoromethoxyphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-trifluoromethoxyphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,4-dichlorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,4-dibromophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,4-difluorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,5-dichlorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,5-dibromophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,5-difluorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,4-dimethylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3,5-dimethylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-methyl-4-chlorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methyl-3-chlorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-methyl-4-fluorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methyl-3-fluorophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-methyl-4-bromophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methyl-3-bromophenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-methyl-4-trifluoromethylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methyl-3-trifluoromethylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-methyl-4-trifluoromethoxyphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methyl-3-trifluoromethoxyphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-cyano-4-methylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-cyano-3-methylphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-chloro-4-methoxyphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-chloro-3-methoxyphenyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(2-methylpyridin-6-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(2-methylthiazol-4-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(4-methylthiazol-2-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(2-methylpyridin-3-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(2-methylpyridin-3-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(3-pyridinyl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(5-methylpyridin-3-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-(2-methylpyridin-3-yl)-3-pyridinyl]-2-fluorophenyl methyl sulfone;

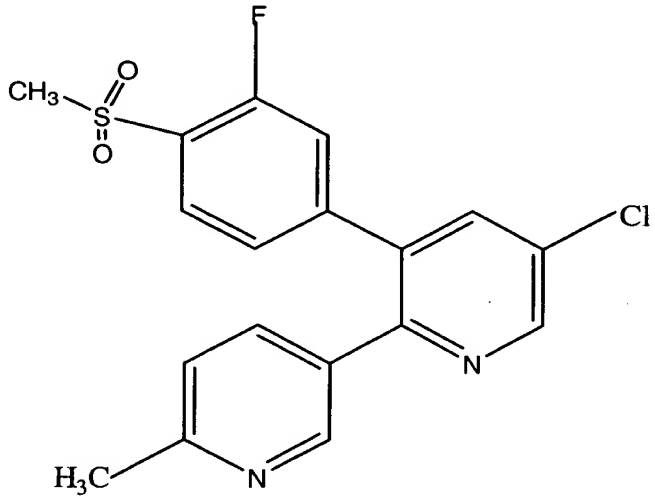
4-[4-cyclohexyl-3-pyridinyl]-2-fluorophenyl methyl sulfone;

4-[4-cyclopentyl-3-pyridinyl]-2-fluorophenyl methyl sulfone;

5-chloro-3-(3-fluoro-4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine;

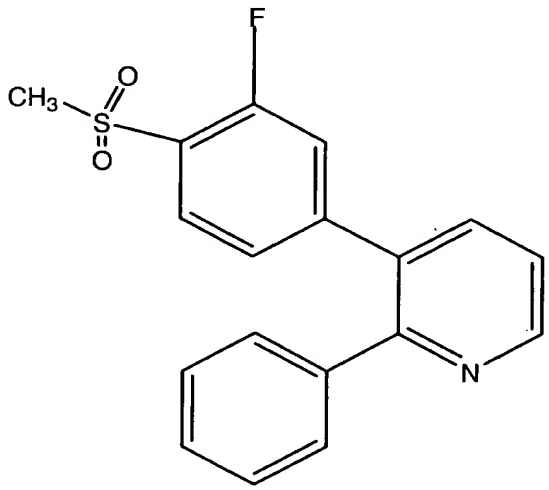
and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

In one embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

In another embodiment, the species is:



and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof. In another embodiment, the fluoro radical is at the meta position relative to the sulfonyl group.

Additional Compounds

Within Formula I there is another subclass of compounds of interest that includes, but is not limited to:

2-fluoro-4-[3-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]- 1,3-thiazol-2(3H)-one;

2-fluoro-4-[3-(4-methylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)- 2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-difluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-thiazol-4-yl]benzenesulfonamide;

3-cyclohexyl-2-oxo-2,3-dihydro-1,3-thiazol-4-yl] benzenesulfonamide;

3-cyclopentyl-2-oxo-2,3-dihydro-1,3-thiazol-4-yl] benzenesulfonamide;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]- 1,3-thiazol-2(3H)-one;;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]- 1,3-thiazol-2(3H)-one;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-thiazol-2(3H)-one;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one; and

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-thiazol-2(3H)-one;

and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Within Formula I there is another subclass of compounds of interest that includes, but is not limited to:

2-fluoro-4-[3-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-chlorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-chlorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-bromophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-bromophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-fluorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-fluorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]- 1,3-oxazol-2(3H)-one;

2-fluoro-4-[3-(4-methylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-cyanophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-cyanophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-dichlorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-dibromophenyl)- 2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-difluorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-dichlorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-dibromophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-difluorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,4-dimethylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3,5-dimethylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-chlorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-chlorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-fluorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-fluorophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-bromophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-bromophenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-methyl-4-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methyl-3-trifluoromethoxyphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-cyano-4-methylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-cyano-3-methylphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-chloro-4-methoxyphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-chloro-3-methoxyphenyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-6-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylthiazol-4-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(4-methylthiazol-2-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(3-pyridinyl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(5-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

2-fluoro-4-[3-(2-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzenesulfonamide;

3-cyclohexyl-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzene-sulfonamide;

3-cyclopentyl-2-oxo-2,3-dihydro-1,3-oxazol-4-yl]benzene-sulfonamide;

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-1,3-oxazol-2(3H)-one;

3-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,4-dibromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]- 1,3-oxazol-2(3H)-one;

3-(3,4-difluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,5-dibromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,5-difluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one; and

3-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-1,3-oxazol-2(3H)-one;

and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Within Formula I there is another subclass of compounds of interest that includes, but is not limited to:

5-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]- 2-(difluoromethyl)-1H-imidazole;

5-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]- 2-(difluoromethyl)-1H-imidazole;

5-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methyl-sulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(difluoromethyl)-1H-imidazole;

5-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-chlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]- 2-(trifluoromethyl)-1H-imidazole;

5-(4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-cyanophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,4-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,4-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]- 2-(trifluoromethyl)-1H-imidazole;

5-(3,4-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,5-dichlorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,5-dibromophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,5-difluorophenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,4-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3,5-dimethylphenyl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-methyl-4-chlorophenyl)-4-[3-fluoro-4-methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-methyl-3-chlorophenyl)-4-[3-fluoro-4-methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-methyl-4-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-methyl-3-fluorophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-methyl-4-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-methyl-3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-methyl-4-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-methyl-3-trifluoromethylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-methyl-4-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-methyl-3-trifluoromethoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-cyano-4-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-cyano-3-methylphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-chloro-4-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-chloro-3-methoxyphenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(2-methylpyridin-6-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(2-methylthiazol-4-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(4-methylthiazol-2-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(3-pyridinyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(5-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-(2-methylpyridin-3-yl)-4-[3-fluoro-4-(methylsulfonyl) phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

5-cyclopentyl-4-[3-fluoro-4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1H-imidazole;

and the pharmaceutically-acceptable salts, tautomers and prodrugs thereof.

Definitions

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl" and "alkoxyalkyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. Even more preferred are lower alkyl radicals having one to three carbon atoms.

Where the term "alkenyl" is used, either alone or within other terms such as "arylalkenyl", it embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl

radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkenyl" embraces partially saturated carbocyclic radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are partially saturated carbocyclic radicals that contain two double bonds (that may or may not be conjugated) can be called "cycloalkyldienyl". More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term "halo" and "halogen" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The terms "hydroxyalkyl" and "hydroxylalkyl" embrace linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and

hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "cyanoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more cyano radicals. More preferred cyanoalkyl radicals are "lower cyanoalkyl" radicals having one to six carbon atoms and one cyano radical. Even more preferred are lower cyanoalkyl radicals having one to three carbon atoms. Examples of such radicals include cyanomethyl.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. More preferred aryl is phenyl. Said "aryl" group may have one to three substituents such as lower alkyl, hydroxy, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino.

The term "heterocyclyl" or "heterocyclo" embraces 3-10 membered saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. More preferred heterocyclyl are 5-8 membered ring heterocyclyl. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, for example, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen

atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl]; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino.

Heterocyclic radicals can include 3-10 membered fused or unfused radicals. Preferred examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, furyl, and pyrazinyl. More preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur nitrogen and oxygen, selected from thienyl, furanyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are lower aralkyl radicals having phenyl attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "arylalkenyl" embraces aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having two to six carbon atoms. Examples of such radicals include phenylethenyl. The aryl in said

arylalkenyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The aryl in said aralkyl and arylalkenyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The terms benzyl and phenylmethyl are interchangeable.

The term "heterocyclylalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6- membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6- membered heteroaryl radical. Even more preferred are lower heteroarylalkyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals.

The term "aryloxy" embraces aryl radicals attached through an oxygen atom to other radicals. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aryloxyalkyl" embraces aryloxy radicals as described above attached through the oxygen atom to an alkyl radical. The term "heterocyclyloxy" embraces heterocyclyl radicals attached through an oxygen atom to other radicals.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom. More preferred are lower alkylsulfinyl radicals having one to three carbon atoms.

The term "sulfonyl", whether used alone or linked to other terms such as "alkylsulfonyl" and "arylsulfonyl", denotes respectively divalent radicals $-SO_2-$.

"Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylsulfonyl radicals having one to three carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. "Arylsulfonyl" embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. A preferred arylsulfonyl radical is phenylsulfonyl.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" where sulfamyl radicals are substituted, respectively, with one alkyl radical, or two alkyl radicals. More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl. The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. More preferred N-alkyl-N-arylaminosulfonyl radicals are "lower N-alkyl-N-arylsulfonyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower N-alkyl-N-arylsulfonyl radicals having one to three carbon atoms. Examples of such lower N-alkyl-N-aryl-aminosulfonyl radicals include N-methyl-N-phenylaminosulfonyl and N-ethyl-N-phenylaminosulfonyl. Examples of such N-aryl-aminosulfonyl radicals include N-phenylaminosulfonyl.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH_3-S-). The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals

having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio. The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C_1-C_3-alkylthio radicals. An example of "aralkylthio" is benzylthio. The term "arylthioalkyl" embraces arylthio radicals as described above, through the sulfur atom to an alkyl radical.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO_2H. The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical.

The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes -(C=O)-.

The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylcarbonyl radicals having one to three carbon atoms. The term "alkylcarbonyl" includes radicals having alkyl, hydroxylalkyl, radicals, as defined herein, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl.

The term "arylcarbonyl" embraces radicals having a carbonyl radical substituted with an aryl radical. More preferred arylcarbonyl radicals include phenylcarbonyl. The term "arylalkylcarbonyl" embraces radicals having a carbonyl radical substituted with an arylalkyl radical. More preferred radicals are phenyl-C_1-C_3-alkylcarbonyl, including benzylcarbonyl.

The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted

methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. Even more preferred are lower alkoxycarbonyl radicals having alkoxy portions of one to three carbon atoms. The term "alkoxycarbonylalkyl" embraces alkyl radicals substituted with an alkoxycarbonyl radical as defined above. More preferred are "lower alkoxycarbonylalkyl" radicals with alkyl portions having one to six carbons. Examples of such lower alkoxycarbonylalkyl radicals include substituted or unsubstituted methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl and ethoxycarbonylethyl.

The term "aminocarbonyl" when used by itself or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", denotes an amide group of the formula $-C(=O)NH_2$. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. Even more preferred are lower alkylaminoalkyl radicals having one to three carbon atoms.

The terms "N-alkylamino" and "N,N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals

may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" denotes amino groups that have been substituted with one or two aralkyl radicals. More preferred are phenyl-C_1-C_3-alkylamino radicals, such as N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical. The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminocarbonyl" denotes an amide group of the formula -C(=O)NH2. The term "alkylaminocarbonyl" denotes an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "arylaminoalkyl" embraces radicals having one or more aryl radicals attached to an aminoalkyl radical.

The additional terms used to describe the substituents of the compounds of Formulae I-VII and not specifically defined herein are defined in a similar manner to that illustrated in the above definitions.

The terms "treatment" and "treating" refers to any process, action, application, therapy, or the like, wherein a subject, including a human being, is provided medical aid with the object of improving the subject's condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

The term "prevention" or "prophylaxis" includes either preventing the onset of clinically evident inflammation or inflammation related disorders altogether or preventing the onset of a preclinically evident stage of inflammation or an inflammation related disorder in individuals.

The term "therapeutically-effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in disease severity and the frequency of incidence while avoiding adverse side effects typically associated with alternative therapies.

The term "prodrug" refers to a compound that is a drug precursor that, following administration to a subject and subsequent absorption, is converted to an active species in

vivo via some process, such as metabolic conversion. Other products from the conversion process are easily disposed of by the body. More preferred prodrugs produce products from the conversion process that are generally accepted as safe. By way of illustration and not limitation, U.S. Patent 5,932,598 describes prodrug forms of compounds that are substituted sulfonamide compounds that selectively inhibit cyclooxygenase-2. For example, the prodrug may be an acylated form of the active compound such as an acylated sulfonamide.

The term "co-therapy" (or "combination-therapy"), in defining use of a cyclooxygenase-2 inhibitor agent and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Stereoisomers, Tautomers, Protected Acids and Salts

Also included in the family of compounds of Formulae I through VII are the stereoisomers thereof including, but not limited to enantiomers, diastereomers, racemic mixtures and other mixtures thereof.

Also included in the family of compounds of Formulae I through VII are the tautomeric forms of those compounds.

Also included in the family of compounds of Formulae I through VII are the protected acids thereof, such as the esters, hydroxyamino derivatives, amides and sulfonamides. Thus, for example, primary and secondary amines can be reacted with carboxylic acid substituted forms of Formula I-VII to form amides which can be useful as prodrugs. Preferred amines are heterocyclicamines, including optionally substituted aminothiazoles, optionally substituted amino-isoxazoles, and optionally substituted aminopyridines; aniline derivatives; sulfonamides; aminocarboxylic acids; and the like. The esters, hydroxyamino derivatives and sulfonamides can be prepared from the acids by methods known to one skilled in the art.

Also included in the family of compounds of Formulae I-VII are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts"

embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulae I-VII may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, N-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulae I-VII include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compounds of the invention by reacting, for example, the appropriate acid or base with the compounds of Formulae I-VII.

Pharmaceutical Compositions

Also embraced within this invention is a class of pharmaceutical compositions comprising the one or more of the active compounds of Formulae I-VII in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions may, for example, be administered orally, pulmonary, mucosally,

intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of

the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

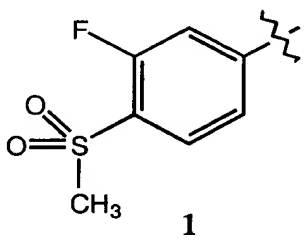
For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

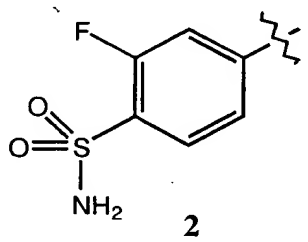
General Synthetic Procedures

The compounds of the invention can be synthesized according to the procedures set forth below. The substituents of the compounds shown in the following procedures generally have the same definition as the substituents at the corresponding position in the compounds of Formulae I-VII, except where further noted. For example, unless otherwise noted, R^1, R^2 and R^3 as used in the procedures below correspond to R^1, R^2 and R^3 as

previously defined; R^{3A} and R^{3B} correspond to substituents independently selected from R^3 as previously defined; and R^S corresponds to a functional group selected from the group consisting of hydrogen and the optional substituents previously defined for the R^1 cyclohexyl, pyridinyl and phenyl moieties. Unless otherwise noted, X as used in the procedures below corresponds to halogen.

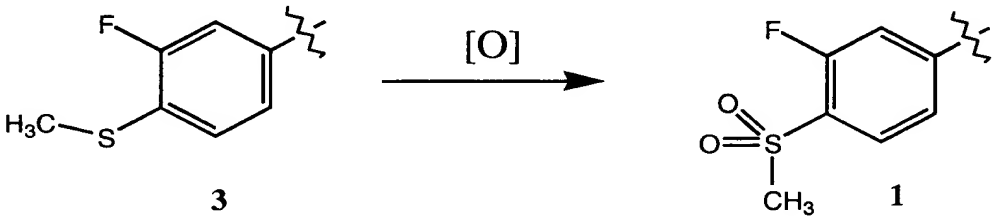


1



2

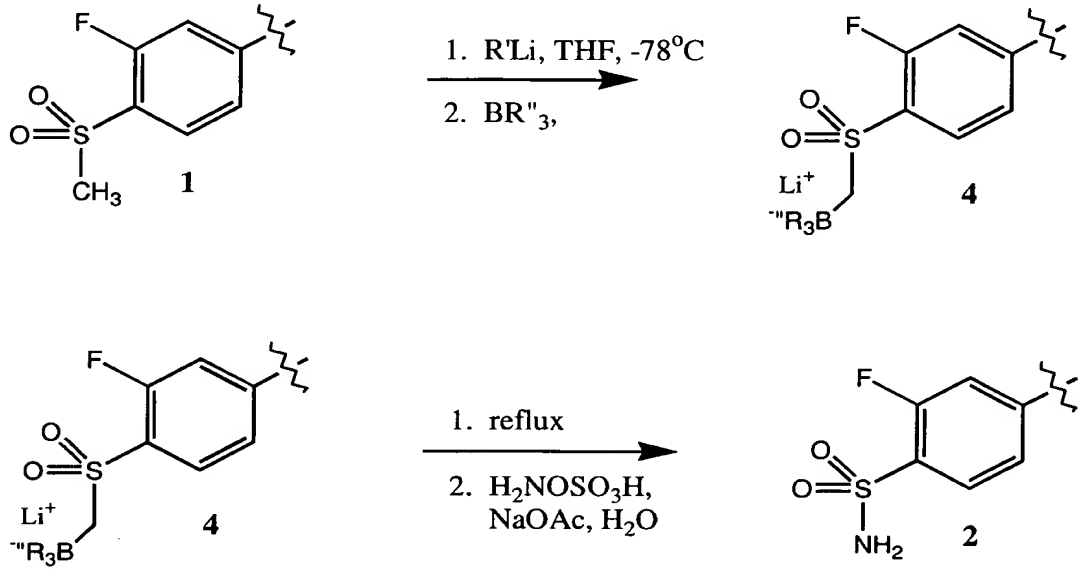
The 3-fluoro-4-methylsulfonylphenyl **1** and 3-fluoro-4-aminosulfonylphenyl **2** are specific regiochemically substituted aromatic rings present in the cyclooxygenase-2 inhibiting diaryl-heterocycles disclosed in this application. The described 3-fluoro-4-methyl-sulfonyphenyl **1** and 3-fluoro-4-amino-sulfonylphenyl **2** ring functionality can be prepared using the synthetic methodology outlined below for the various diaryl substituted heterocycles disclosed in this application.



3 1

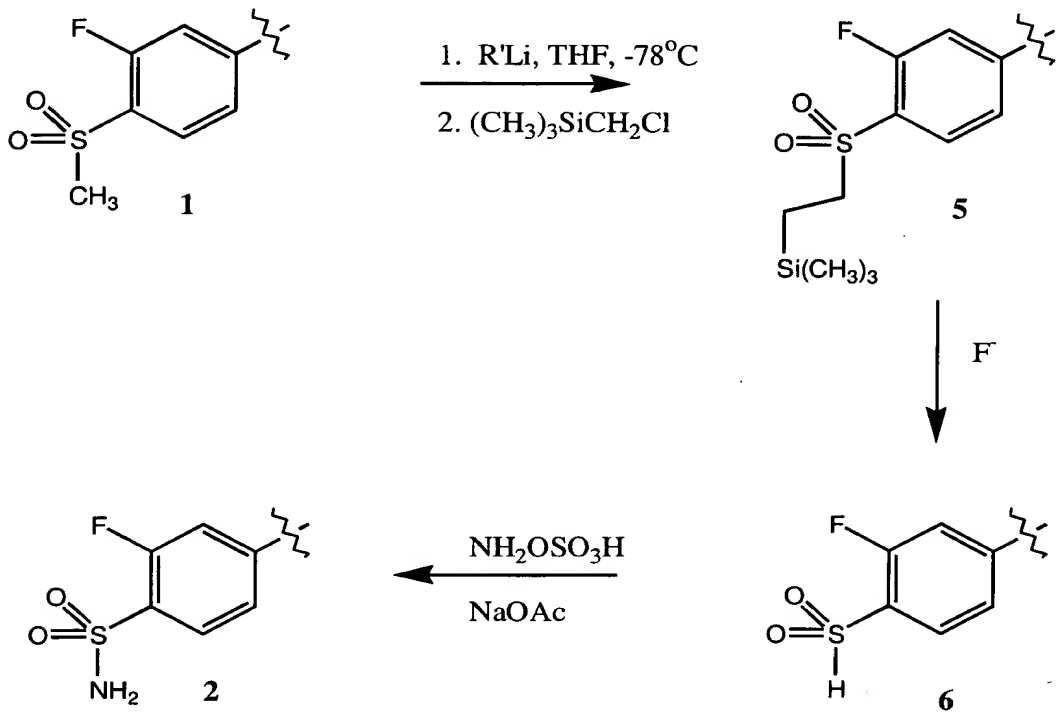
The methythio **3** group can be converted to the methylsulfone **1** through treatment with at least two molar oxidizing equivalents of reagents such as *m*-chloroperbenzoic acid, monoperoxyphthalic acid, peroxides, or OXONE®.

Scheme I



The sulfonamide **2** can be obtained from the sulfone **1** by treatment with an alkyl base such as butyllithium, methyllithium, and the like in ethereal solvents such as tetrahydrofuran at approximately -78°C. In a second step, a trialkyl-borane, such as triethylborane or tributylborane, is added affording the intermediate borate **4** which is warmed to room temperature prior to refluxing for 16 hours or an appropriate period of time. The solution is cooled to room temperature and water, sodium acetate and hydroxylamine-*O*-sulfonic acid are added to yield the sufonamide **2** [Huang; *Tetrahedron Letters*, *35*, 7201-7204(1994)].

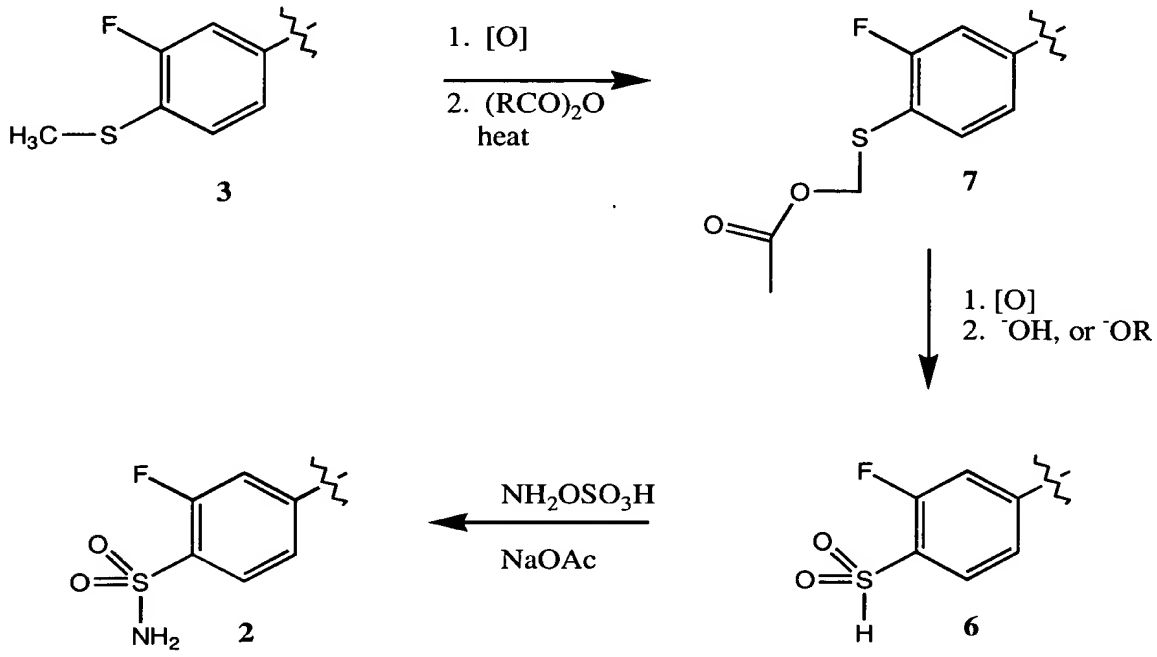
Scheme II



In **Scheme II**, the sulfonamide **2** can be obtained by treatment of the sulfone **1** with an alkyl base such as butyllithium. Addition of trimethylsilyl-methylchloride affords the trimethylsilylethylsulfone **5**. Desilylation by the addition of a reagent such as tetra-n-butyl ammonium fluoride to a solution of the sulfone **5** followed by *in situ* ethylene extrusion affords the sulfinic acid **6** [Vhu; *Steriods*, *67*, 543-545 (1997)]. The sulfinic acid **6** can be converted to the sulfonamide **2** by the addition of sodium acetate and hydroxylamine-*O*-sulfonic acid.

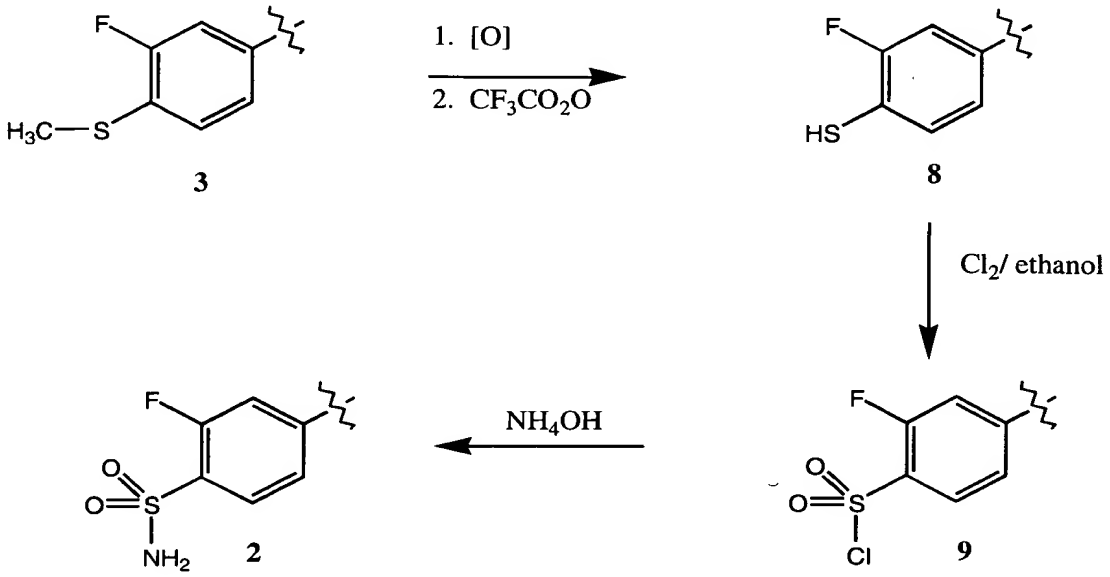
126

Scheme III

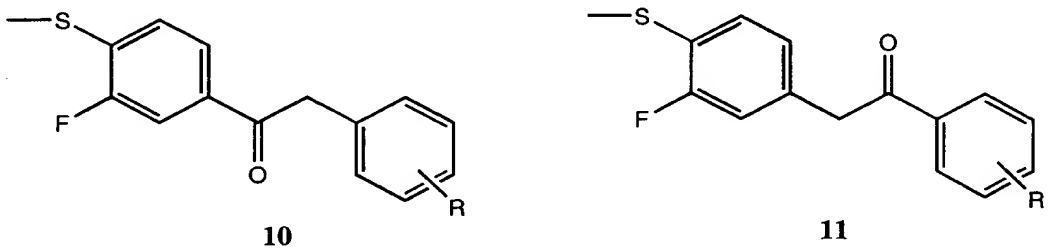


In **Scheme III** sulfonamides **2** can be prepared from the methylthio group **3** by conversion of the methythio moiety to the sulfoxide by careful addition of one equivalent of an oxidizing agent such as *m*-chloroperbenzoic acid, monoperoxyphthalic acid, a peroxide, or OXONE®. A Pummer rearrangement performed by mixing the resulting sulfoxide in anhydrides followed by heating provides the thioacetal **7**. Oxidation to the sulfone as described earlier followed by treatment with either hydroxide or alkoxides provides sulfinic acid **6** [Vleeschauwer; *Syn. Lett.*, 4, 375-377, (1997)] which can be converted to the sulfonamide **2** by the addition of a suitable base such as sodium acetate and hydroxylamine-*O*-sulfonic acid in aqueous alcoholic solvents such as methanol-water or ethanol-water.

Scheme IV



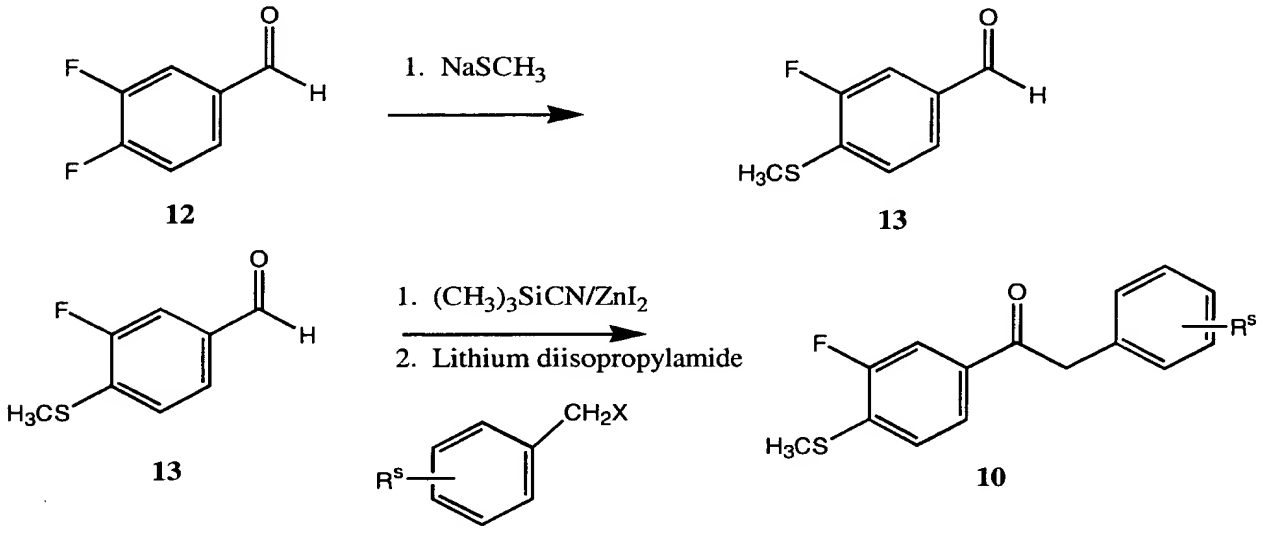
Alternatively, **Scheme IV** illustrates yet another procedure for the preparation of the sulfonamide **2** starting with the corresponding methylthio moiety. First, conversion of the methythio **3** moiety to the methylsulfoxide is accomplished by careful addition of one equivalent of an oxidizing agent such as *m*-chloro-perbenzoic acid, monoperoxyphthalic acid, a peroxide, or OXONE®. The methylsulfoxide is then mixed in a variety of inert solvents such as dichloromethane with trifluoroacetic anhydride which, after aqueous workup, provides the sulfide **8**. The sulfide **8** is treated with chlorine providing the sulfonylchloride **9.** Finally, addition of ammonia to the sulfonylchloride **9** affords the desired sulfonamide **2** [Kharash, J. Am. Chem. Soc., **73**, 3240 (1951)].



3-Fluoro-4-methylthiophenyl-substituted-phenyl-ethanones **10** and **11** are intermediates used in the preparation of many of the diaryl-heterocycles disclosed in this

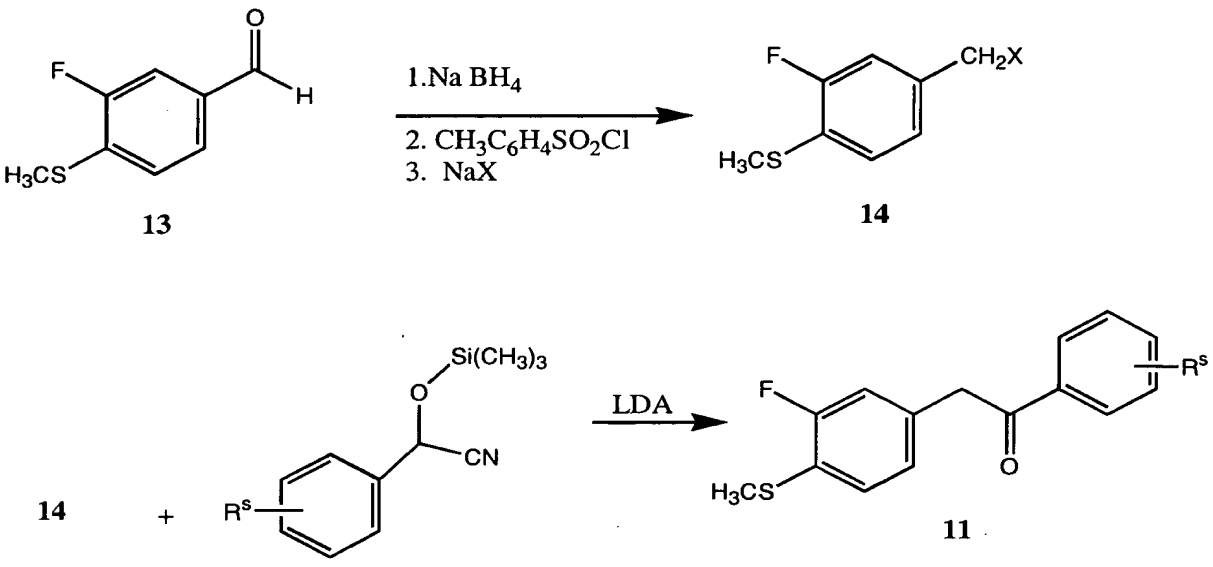
application. The following discussion illustrates representative methods for the preparation of these intermediates.

Scheme V



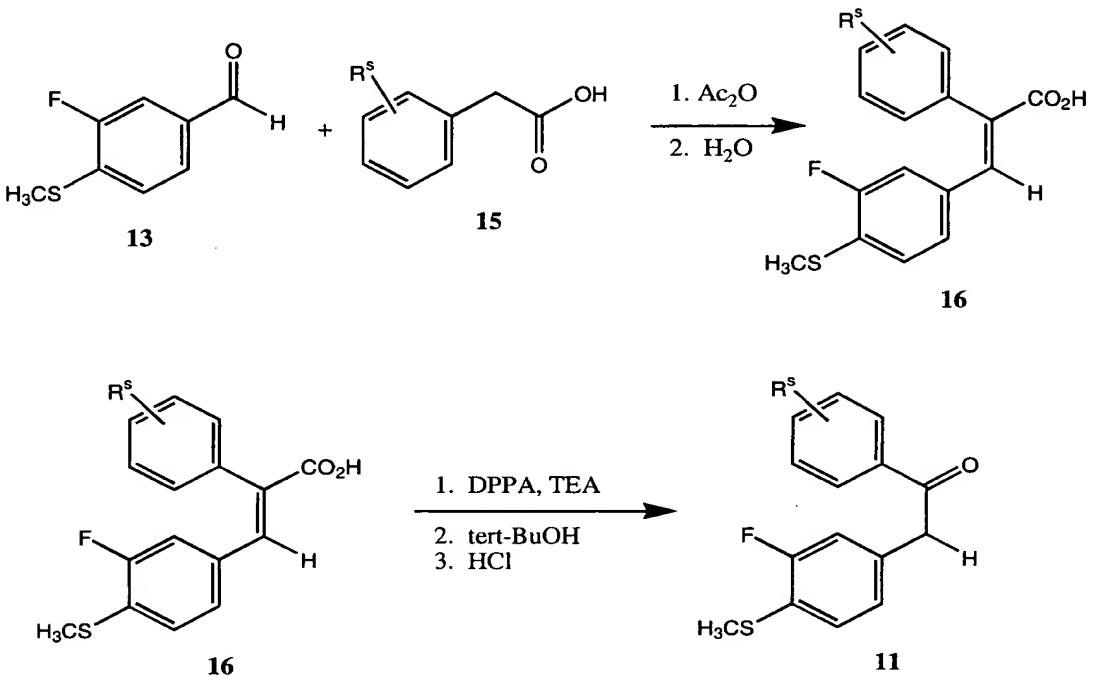
Scheme V outlines a preparation of a deoxybenzoin **10**. Mixing commercially available 3,4-difluorobenzaldehyde **12** with sodium thiomethoxide in polar solvents such as acetonitrile or dimethylformamide produces the 3-fluoro-4-methylthio-benzldehyde **13**. A solution of the aldehyde, zinc iodide, and trimethylsilyl cyanide in a halogenated solvent such as dichloromethane is mixed at room temperature to afford a trimethylsilylcyanohydrin. Deprotonation of the cyanohydrin with a base such as lithium diisopropylamide or lithium hexamethyl-disilylamide followed by addition of an appropriately substituted benzylhalide and acid-base workup of the reaction yields the 1-(3-fluoro-4-methylthiophenyl)-2-(substituted- phenyl)-ethanone **10**.

Scheme VI



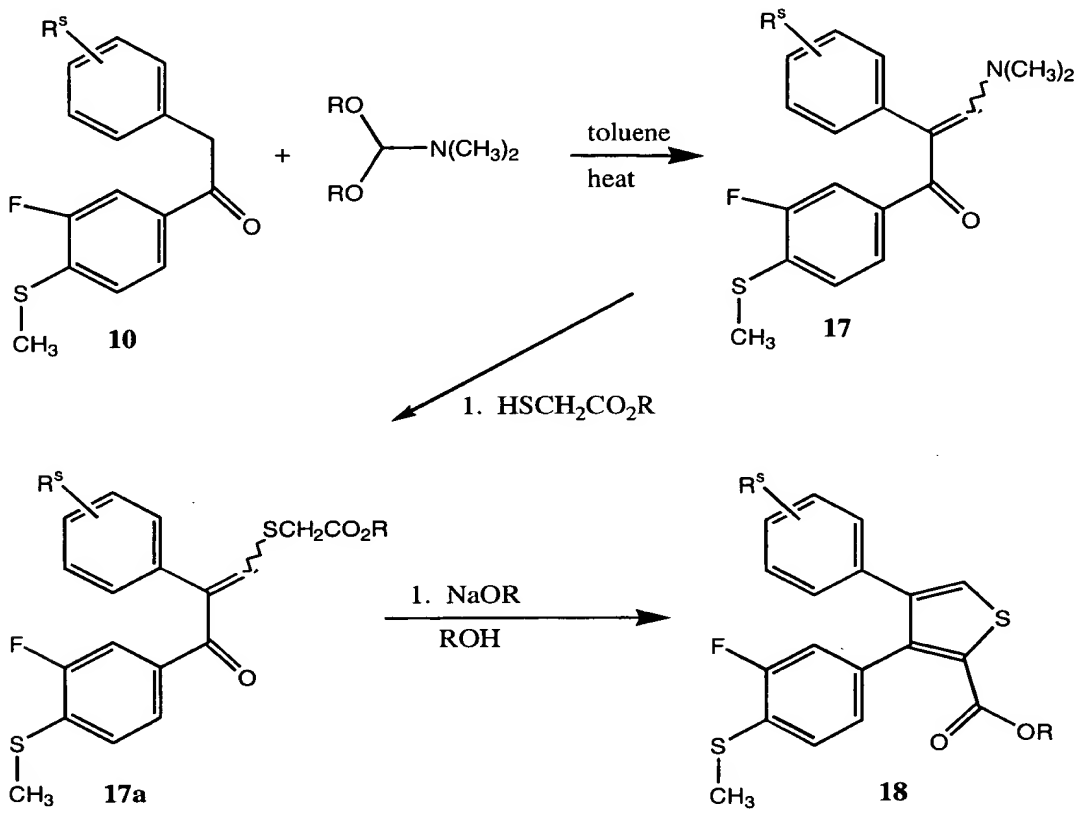
A synthetic scheme for the preparation the 3-fluoro-4-methylthiophenyl-substituted-phenyl-ethanone **11**, which have the alternative regiochemistry, is outlined in **Scheme VI**. Reduction of the 3-fluoro-4-methylthiobenzaldehyde **13** with hydride reagents such as sodium borohydride, lithium aluminum hydride, and the like affords the benzyl alcohol. Conversion of benzyl alcohol to a benzyl halide **14** can be accomplished through the preparation of the tosylate followed by displacement with chloride or bromide ion (represented by X in **Scheme VI**). These compounds can be utilized in the synthetic methodology described previously to afford 1-(substituted-phenyl)-2-(3-fluoro-4-methylthiophenyl)-ethanone **11**.

Scheme VII



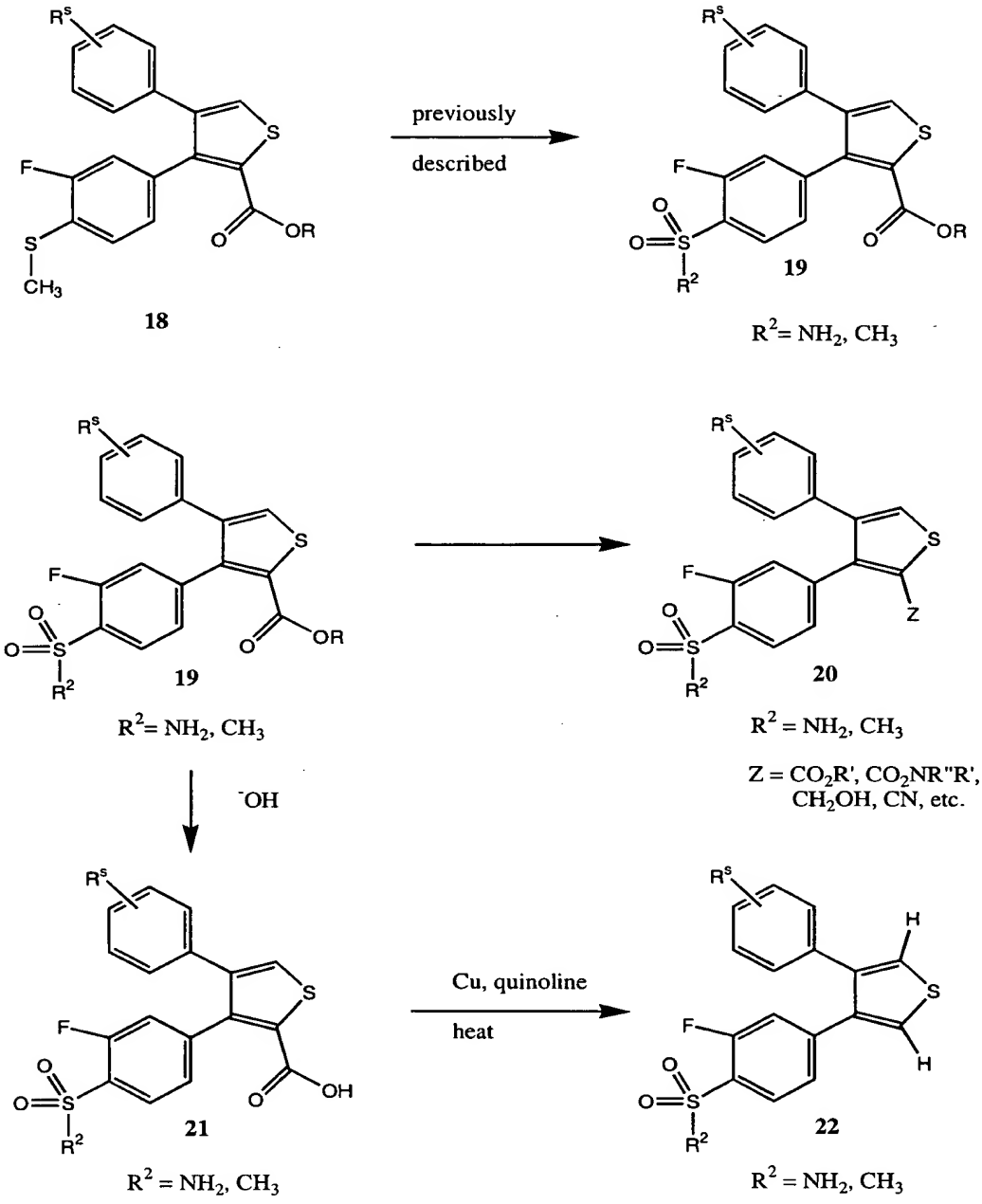
Scheme VII illustrates a procedure that can be used to prepare the 1-(substituted-phenyl)-2-(3-fluoro-4-methylthiophenyl)-ethanone **11** from the 3-fluoro-4-methylthiobenzaldehyde **13**. In step one, the aldehyde **13** and substituted phenylacetic acid **15** are heated in acetic anhydride and triethylamine which, upon aqueous quenching, affords the 2,3-disubstituted acrylic acid **16**. Mixing of the acrylic acid **16** with diphenylphosphorylazide (DPPA) and triethylamine produces an acylazide. The acylazide undergoes a Curtius rearrangement to an isocyanate which is trapped with *tert*-butanol yielding an N-*tert*-butylcarboxy-carbamate. Treatment of the carbamate with concentrated aqueous hydrochloric acid provides the substituted ketone **11**.

Scheme VIII



The preparation of 3,4-diarylthiophene **18** is illustrated in **Scheme VIII**. 3-Fluoro-4-methylthiophenyl-substituted-phenyl ethanone **10** and an acetal of dimethylformamide are refluxed together in toluene. Upon removal of the solvent and excess acetal, the enamine **17** is obtained. The enamine **17** is refluxed in 1,2 dichloroethane with esters of thioacetic acid affording the mixture of Michael addition products **17a**. The 1,2-dichloroethane is removed at reduced pressure and the residue is taken up in an alcoholic solvent and the related sodium alkoxide added. Upon mixing at room temperature the desired trisubstituted thiophene **18** is obtained after purification.

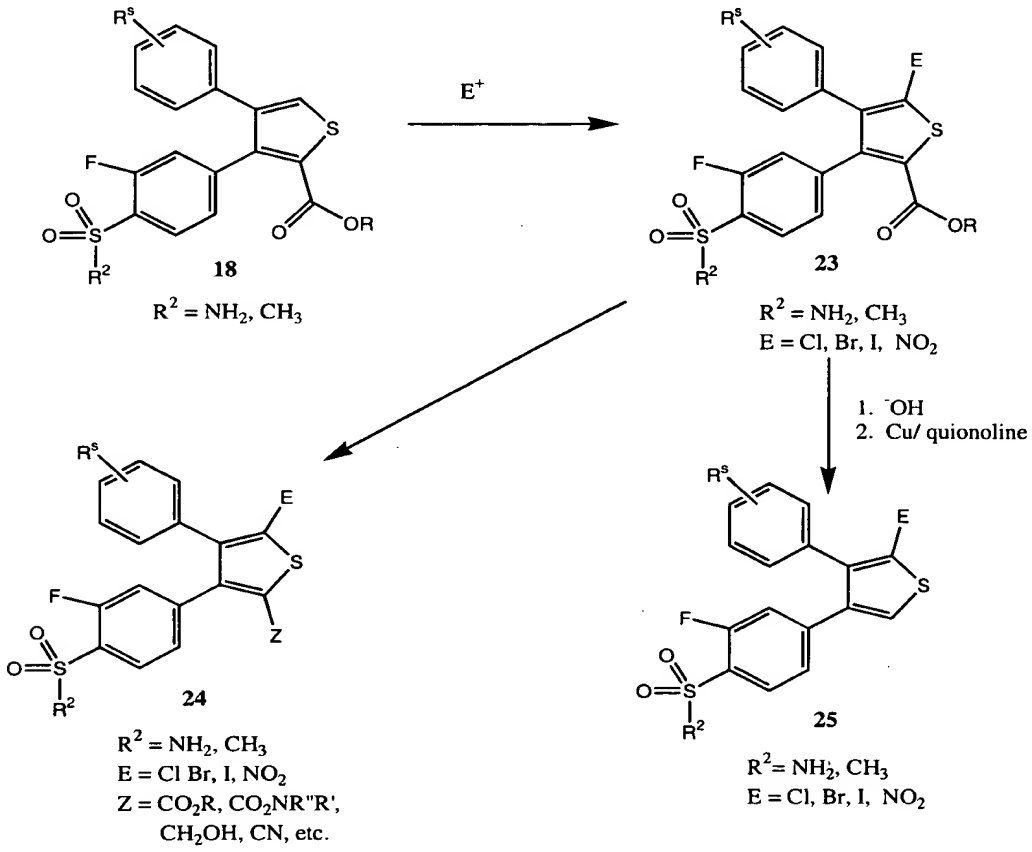
Scheme IX



As illustrated in **Scheme IX**, the methylthiomoiety **18** can be converted to the methyl sulphone and sulfonamide **19** as described previously. The ester group of thiophene **19** can then be manipulated using conventional organic laboratory procedures into a number of functional groups such as alcohol, alkyl, alkenyl, alkynyl, amide, cyano, etc. The ester

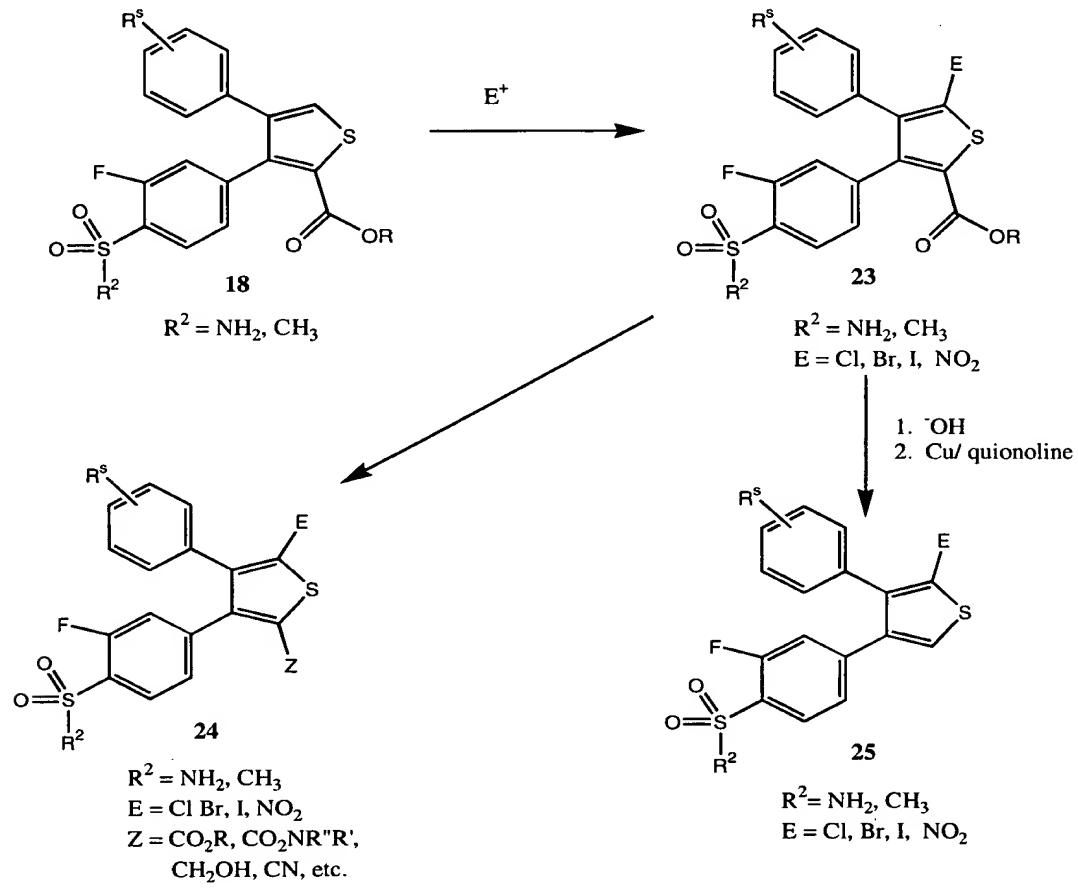
group also can be saponified and the resulting carboxylic acid **21** removed through a copper mediated decarboxylation affording the 3-4 substituted diphenylthiophenes **22**.

Scheme X



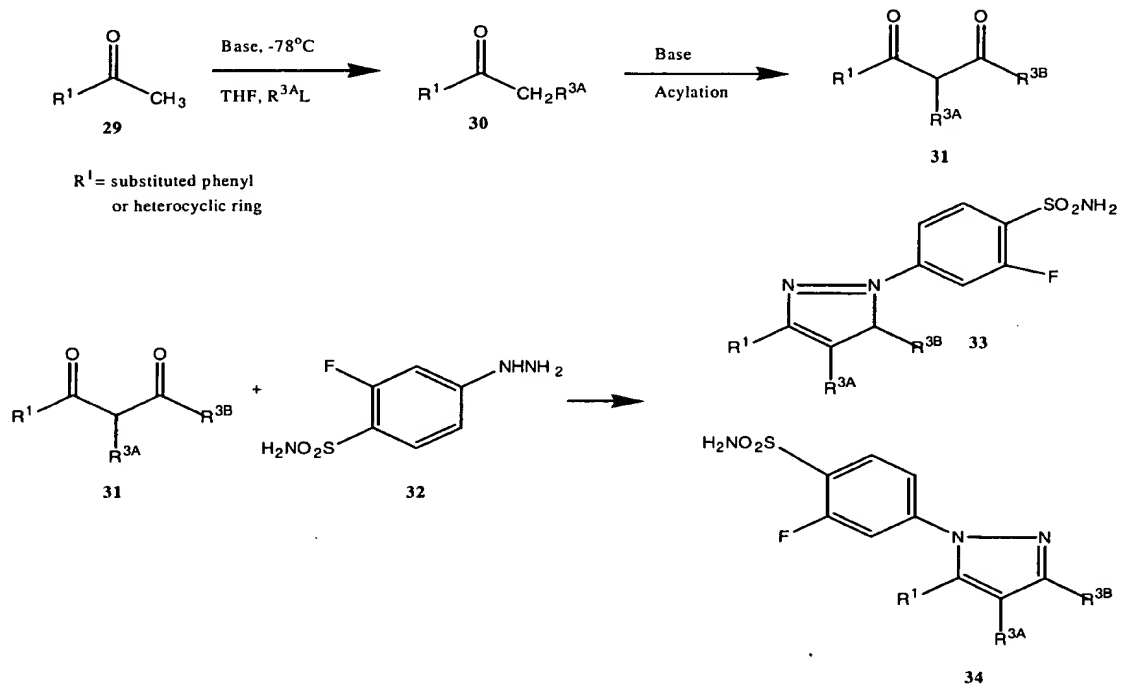
Alternatively, as illustrated in **Scheme X,** the remaining hydrogen of the thiophene ring **18** can be converted to an halogen or nitro group **23** and the ester once more manipulated as described to a variety of functional groups as in structures **24** and **25**.

Scheme XI



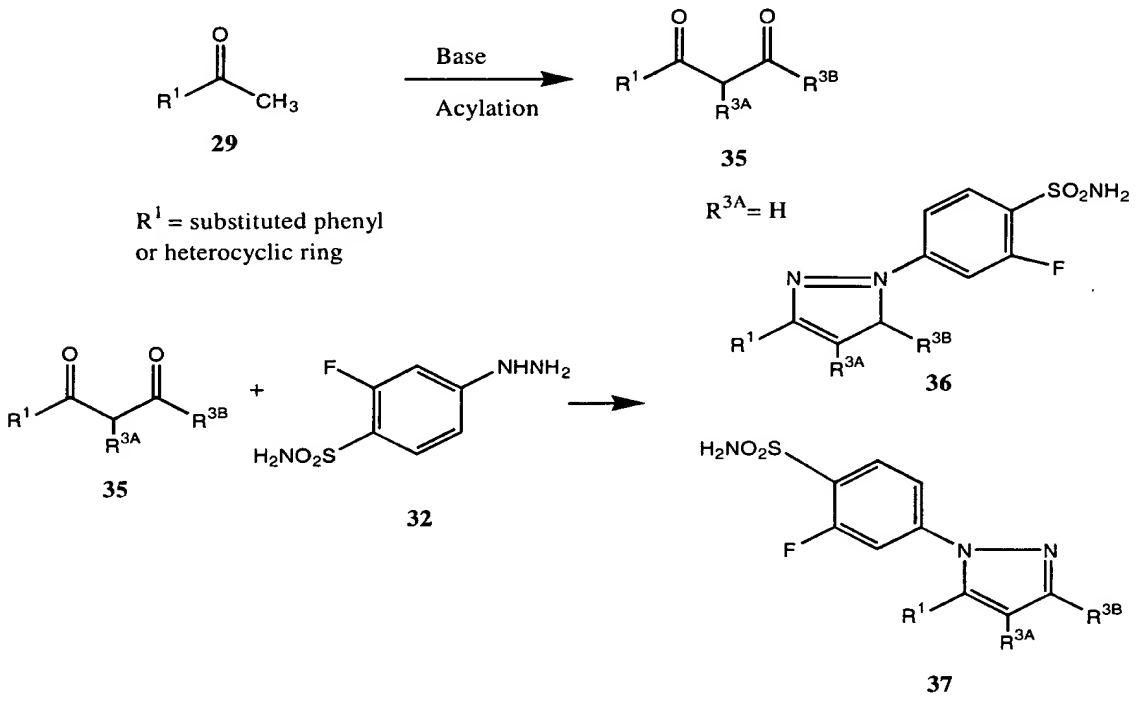
Initiation of the thiophene protocol with the second regioisomer of the 3-fluoro-4-methylthiophenyl-substituted phenyl ethanone **11** and implementation of the thiophene chemistry described in **Scheme X** affords thiophenes with the regiosubstitution shown in **Scheme XI**.

Scheme XII



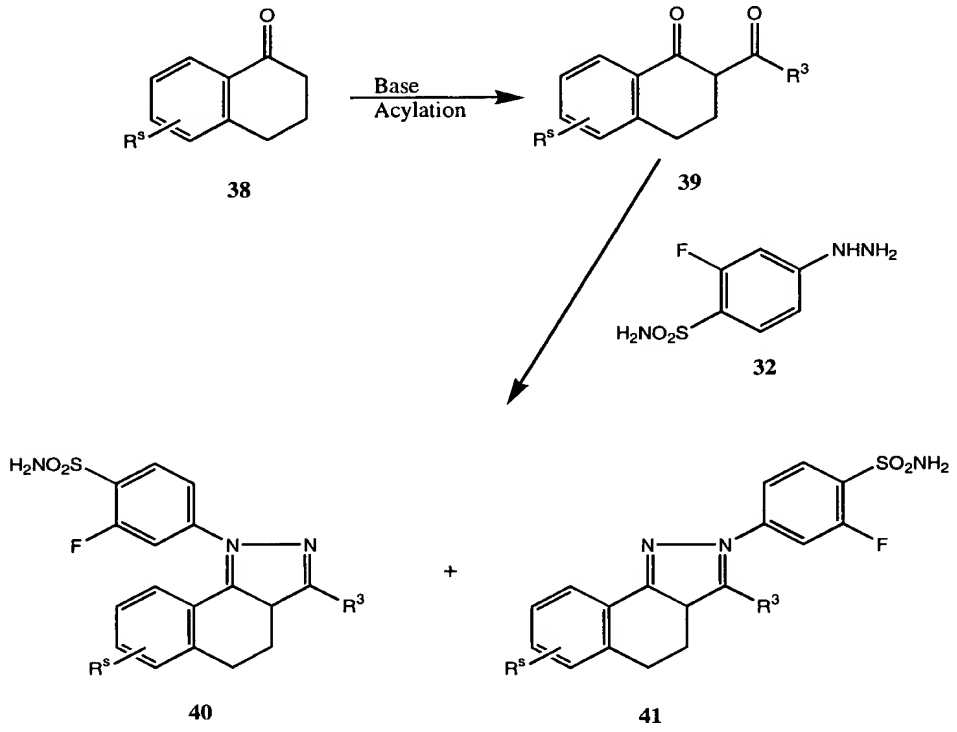
Synthetic **Scheme XII** illustrates the preparation of tetrasubstituted pyrazoles from acetophenone **29**. In step 1 of synthetic **Scheme XII**, the phenyl-methyl ketone **29** is treated with a base and an alkylating reagent (R^3L, where L represents a leaving group such as tosyl) to give the substituted ketone **30.** In step 2, the substituted ketone **30** is treated with base, such as sodium methoxide, and an acylating reagent such as an ester ($R^{3A}CO_2CH_3$), or ester equivalent (R^{3A}CO-imidazole) to give the intermediate diketone **31** [Reid, Calvin; J. *Amer. Chem. Soc.*, **72,** 2948-2952 (1950)]. In step 3, the diketone **31** is reacted with a substituted hydrazine **32** in acetic acid or an alcoholic solvent to give a mixture of pyrazoles **33** and **34**. Separation of the desired pyrazole **34** can be achieved by chromatography or recrystallization.

Scheme XIII



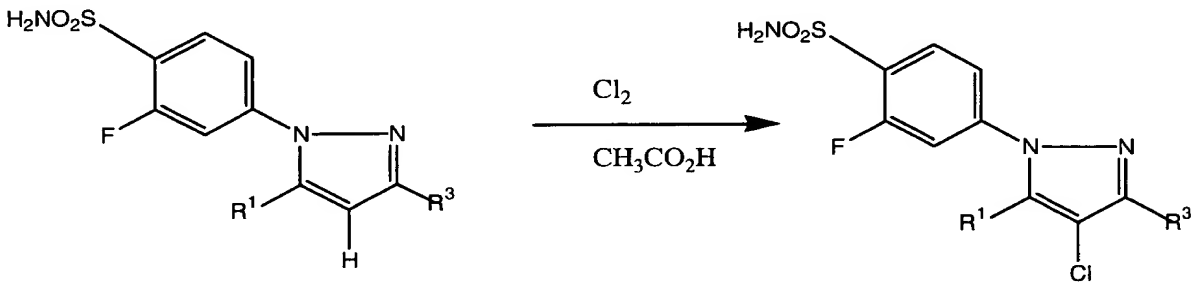
Synthetic **Scheme XIII** illustrates the preparation of 4-unsubstituted-pyrazoles (i.e., R^{3A} as used in Scheme XIII is hydrogen). In step 1, ketone **29** is treated with a base, preferably sodium methoxide or sodium hydride, and an ester, or ester equivalent, to form the intermediate diketone **35** which is used without further purification. In step 2, diketone **35** in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the free base of a substituted hydrazine **32** at reflux for 10 to 24 hours to afford a mixture of pyrazoles **36** and **37.** Recrystallization from diethyl ether/hexane or chromatography affords **37,** usually as a light yellow or tan solid. Additional pyrazoles can be prepared by suitable modification of the methods described in U.S. Patent Nos. 5,401,765, 5,434,178, 4,146,721, 5,051,518, 5,134,142 and 4,914,121 which are incorporated by reference.

Scheme XIV



Synthetic **Scheme XIV** shows an illustrative procedure for the preparation of 4,5-dihydrobenz[g]indazole compounds. In step 1, ethyl esters of acetates are mixed with base, such as 25% sodium methoxide in a protic solvent, such as methanol, and a 1-tetralone derivative **38** to give the intermediate diketone **39**. In step 2, the diketone **39** in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the free base or hydrochloride salt of a substituted hydrazine **32** at reflux for 24 hours to afford a mixture of pyrazoles **40** and **41.** Recrystallization gives the 4,5-dihydro benz[g]lindazolyl-benzenesulfonamide **40**.

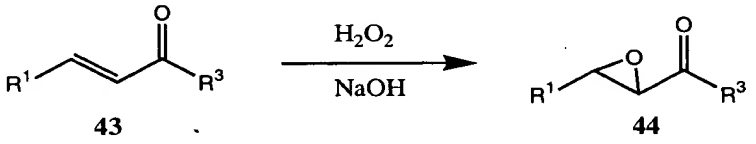
Scheme XV



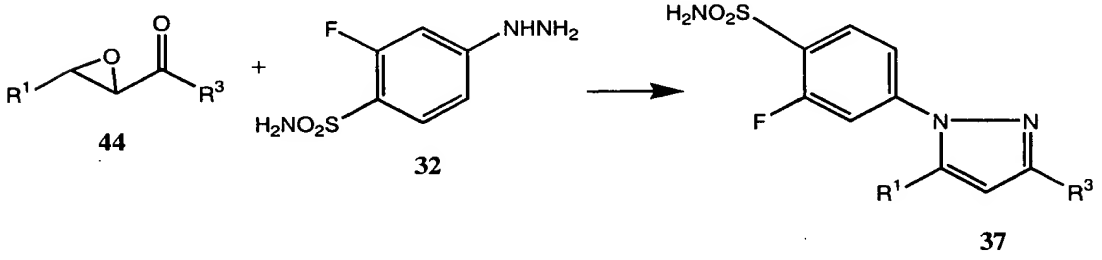
37 **42**

Synthetic **Scheme XV** illustrates the preparation of 4-chloro-pyrazole compound **42** from the pyrazole compound **37**. Chlorination results from passing a stream of chlorine gas at room temperature through a solution containing pyrazole compound **37**.

Scheme XVI



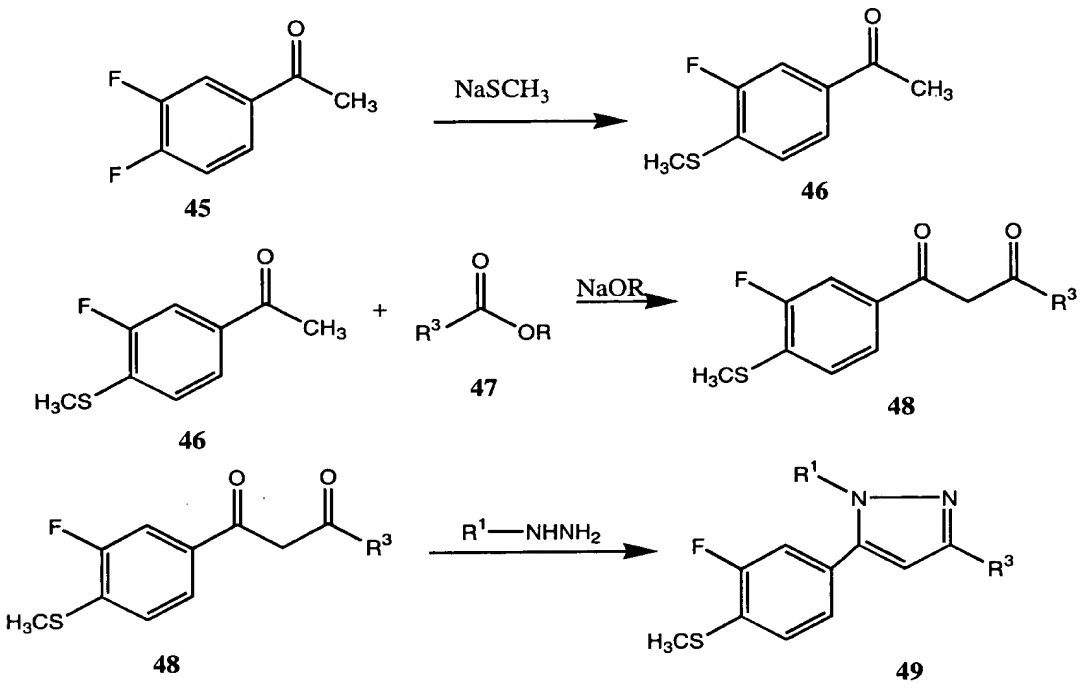
43 **44**



44 **32** **37**

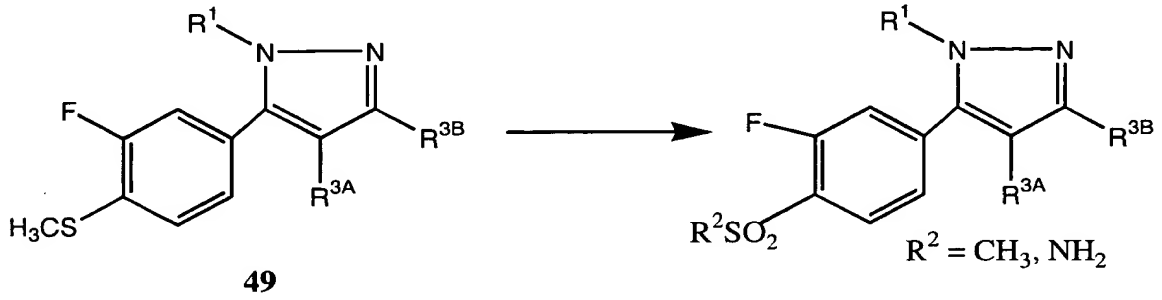
Synthetic **Scheme XVI** illustrates an alternative regioselective method of preparing the pyrazole **37.** Commercially available enones **43** can be epoxidized to give epoxyketones **44,** which are treated with 3-fluoro-4-sulfonamidophenylhydrazine hydrochloride to provide the pyrazole **37.**

Scheme XVII



Scheme XVII illustrates a regioselective method of preparing methylthiopyrazole **49**. The difluoro-acetophenone **45** is mixed with sodium thiomethoxide in a polar solvent such as acetonitrile of dimethylformamide to afford the 3-fluoro-4-methyl-sulfonylacetophenone **46**. Mixing the acetophenone **46** with a base, such as sodium methoxide, and an acylating reagent **47** such as an ester ($R^1CO_2CH_3$), or activated ester equivalent (R^1CO-imidazole), gives the intermediate diketone **48** [J. *Amer. Chem. Soc.*, **72,** 2948-2952, (*1950*)]. This diketone **48** is refluxed with a substituted hydrazine in alcoholic solvents under acid conditons to afford the methylthiopyrazoles **49** after purification by chromatography or crystallization.

Scheme XVIII

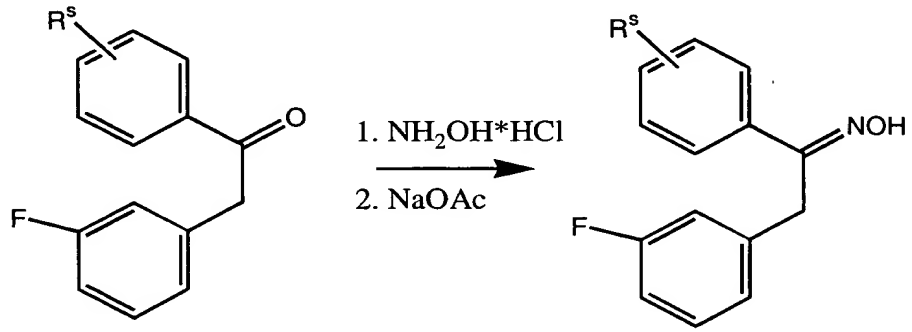


49 **50**

The methylthiopyrazole **49** can be converted to the desired 3-fluoro-4-methylsulfonylpyrazole or 3-fluoro-4-sulfonamidylpyrazole **50** using the procedures described earlier. Similar pyrazoles can be prepared by methods described in U.S. Patent No. 5,486,534 which is incorporated by reference.

WO96/37476 describes methods for the preparation of 3-haloalkyl-1H-pyrazoles and is incorporated by reference.

Scheme XIX

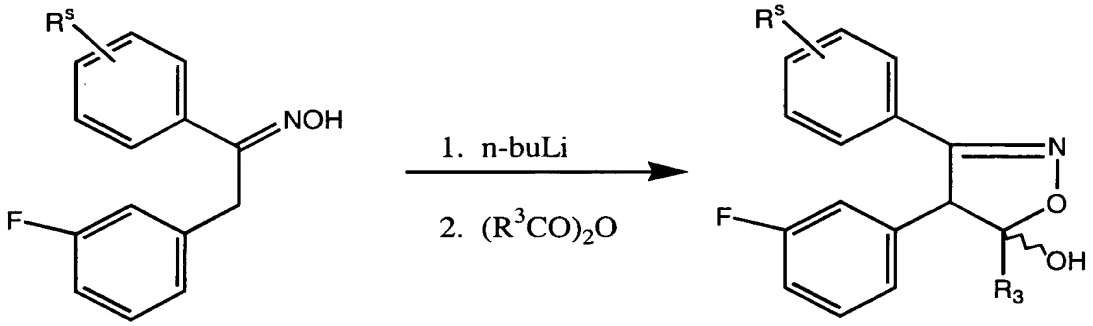


51 **52**

Synthetic **Scheme XIX** illustrates a procedure that can be used for the preparation of oxime intermediate **52.** Treatment of ketone intermediate **51** with hydroxylamine, generally prepared from hydroxylamine hydrochloride by sodium acetate, provides the oxime

intermediate **52.** A wide variety of solvents can be used for this reaction including ethanol, toluene, and tetrahydrofuran.

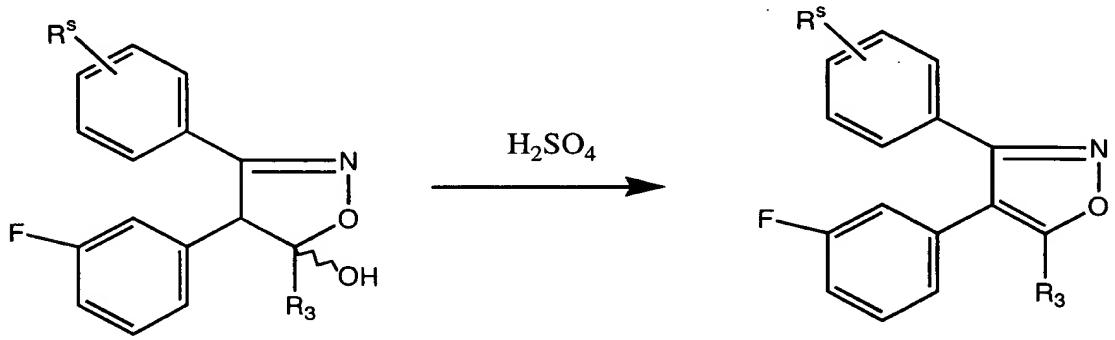
Scheme XX



52 **53**

Synthetic **Scheme XX** illustrates a procedure that can be used for the preparation of hydrated isoxazole derivative **53.** The substituted oxime **52** is treated with at least two equivalents of a base such as n-butyllithium in hexanes to produce a dianion that is subsequently acylated. Suitable acylating agents are anhydrides, acyl imidazoles, esters and the like. Upon quenching the reaction mixture with dilute aqueous acid, hydrated isoxazole derivative **53** can be isolated by crystallization or chromatography.

Scheme XXI

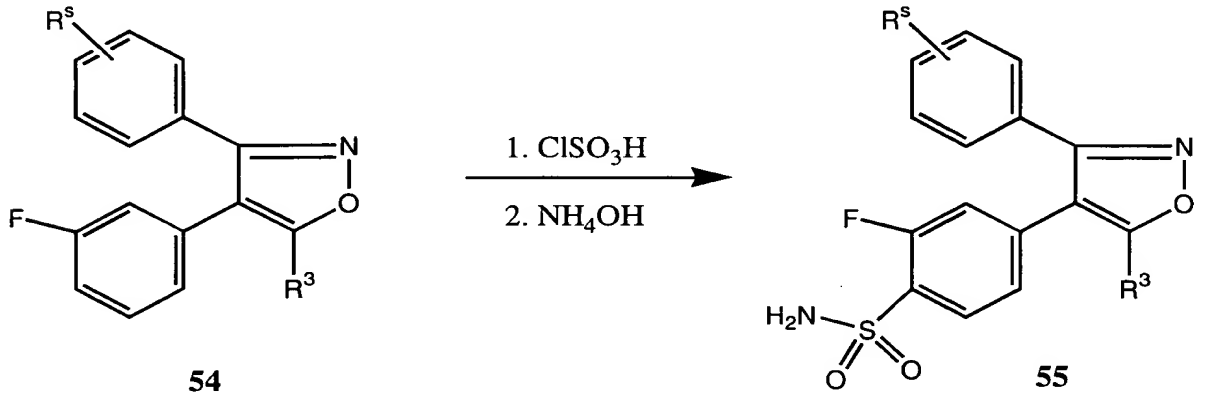


53 **54**

Synthetic **Scheme XXI** illustrates a procedure that can be used for the preparation of isoxazole analog **54** through dehydration of the hydrated isoxazole derivative **53.** Substituted hydrated isoxazole **53** is dissolved in an appropriate solvent such as toluene and

then treated with a catalytic to stochiometric amount of concentrated sulfuric acid to effect dehydration and thereby produce isoxazole derivative **54**. Other acids can also be employed to effect this transformation such as concentrated HCl, concentrated HBr and many others.

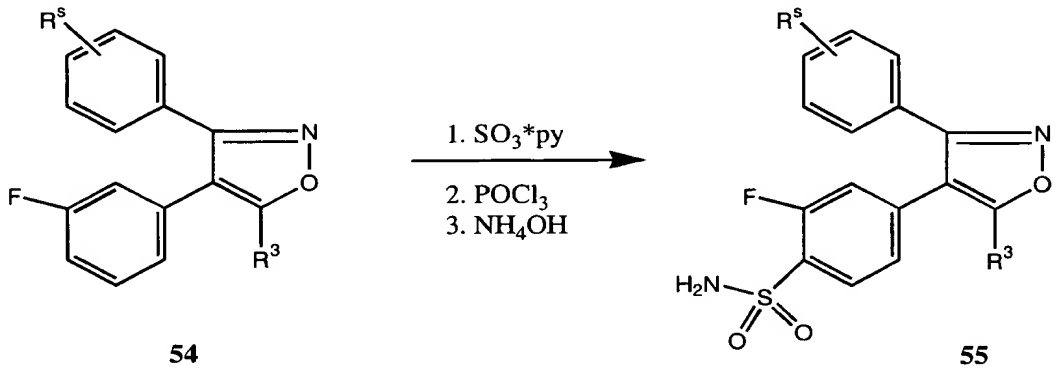
Scheme XXII



54 **55**

Synthetic **Scheme XXII** illustrates a procedure that can be used for the preparation of substituted 3-fluoro-(4-sulfonamidyl)phenylisoxazole analog **55** from the corresponding 3-fluorophenylisoxazole **54.** The procedure is a two step process for the direct introduction of the sulfonamide moiety into 3-fluorophenylisoxazole **54** or hydrated isoxazole **53.** In step one, isoxazole **54** or hydrated isoxazole **53** is treated at about 0° C with two or three equivalents of chlorosulfonic acid to form the corresponding sulfonyl chloride. In step two, the sulfonyl chloride thus formed is treated with concentrated ammonia to provide the sulfonamide derivative **55.**

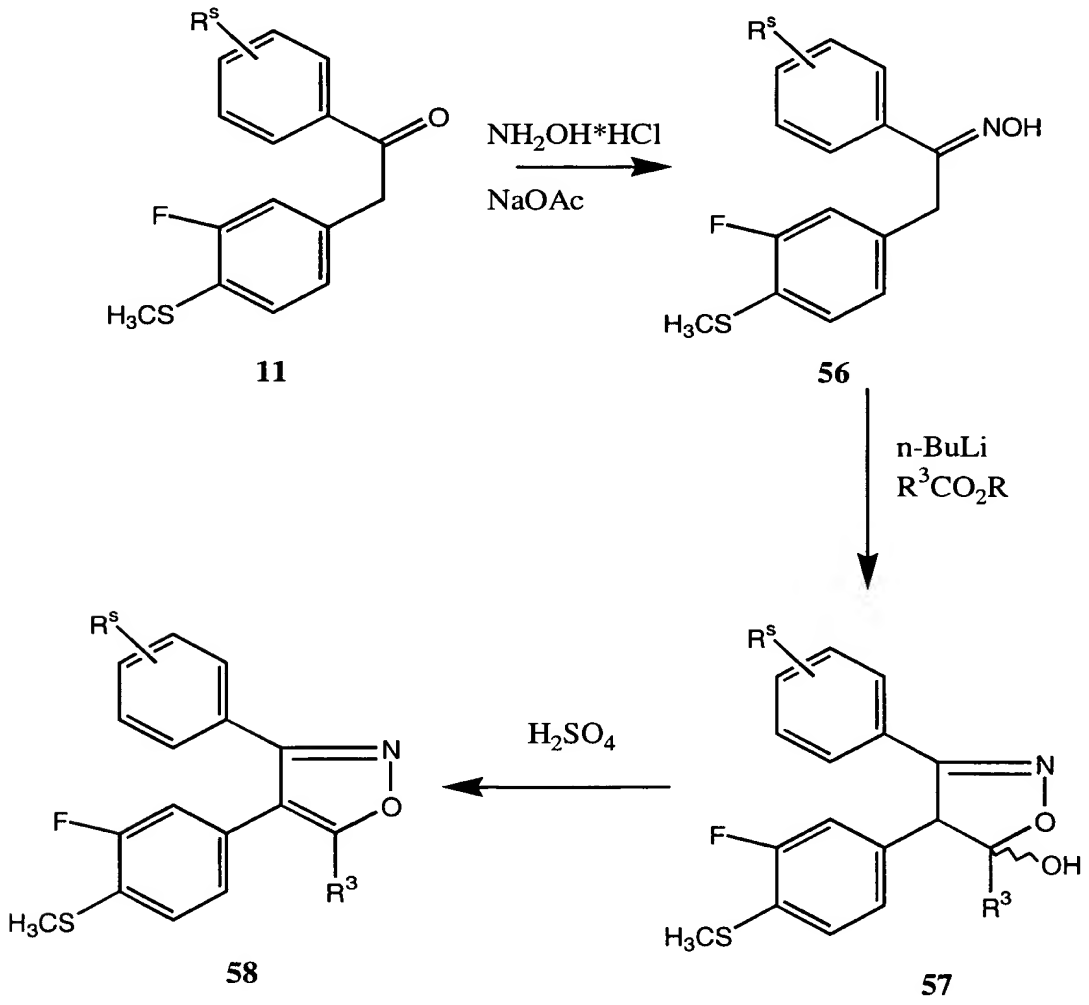
Scheme XXIII



54 **55**

Synthetic Scheme **XXIII** illustrates a three step procedure used to prepare 3-fluoro-4-sulfonamidyl-phenylisoxazole **55** from 3-fluorophenyl isoxazole **54**. In step one, the 3-fluorophenylisoxazole **54** is converted into the corresponding sulfonic acid by treatment with sulfur trioxide pyridine complex at about 100 °C. In step two, the sulfonic acid is converted into the sulfonyl chloride by the action of phosphorus oxychloride. In step three, the sulfonyl chloride is treated with excess concentrated ammonia to provide the 3-fluoro-4-sulfonamidyl-phenylisoxazole **55**.

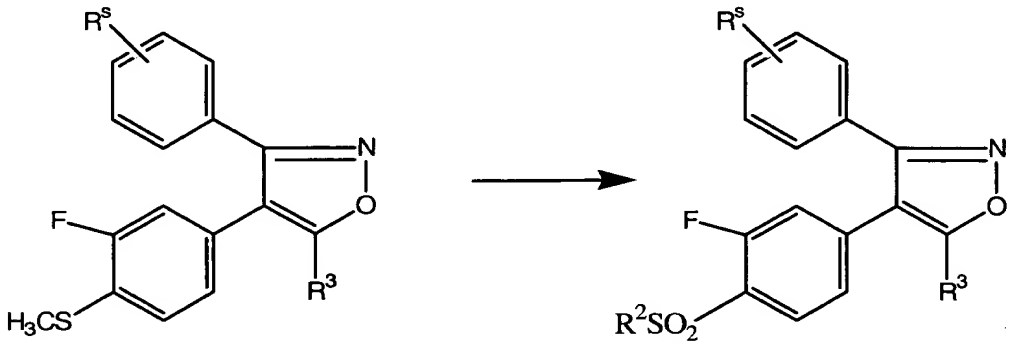
Scheme XXIV



Scheme XXIV illustrates a five step procedure for the preparation of substituted isoxazole derivatives. In step one, substituted 1-substituted phenyl-2-(3-fluoro-4-

methylthiophenyl)-ethanone **11** is converted to the oxime **56** by treatment with hydroxylamine hydrochloride in the presence of sodium acetate in aqueous ethanol. The oxime **56** is treated with slightly more than two equivalents of n-butyl lithium and then the resulting dianion is quenched by a suitable acylating agent such as an anhydride, acid chloride, ester, acyl imidazole and the like to afford hydrated isoxazole **57**. In the last step, the hydrated isoxazole is dehydrated by an acid and the sulfonamide unmasked by treatment with aqueous sulfuric acid to form the isoxazole derivative **58.**

Scheme XXV



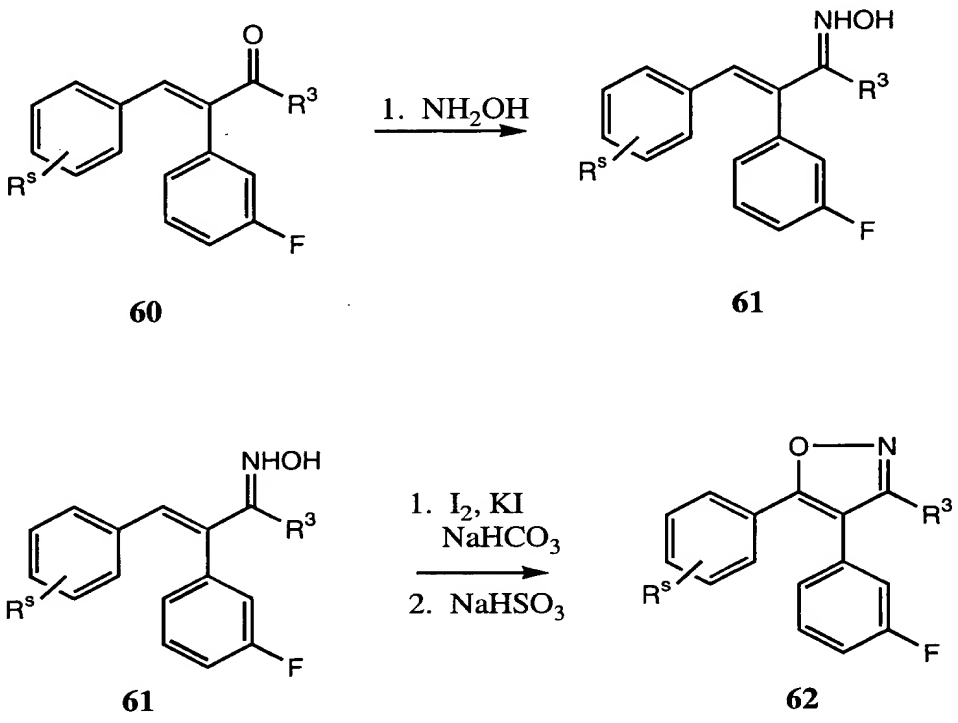
58

$R^2 = CH_3, NH_2$

59

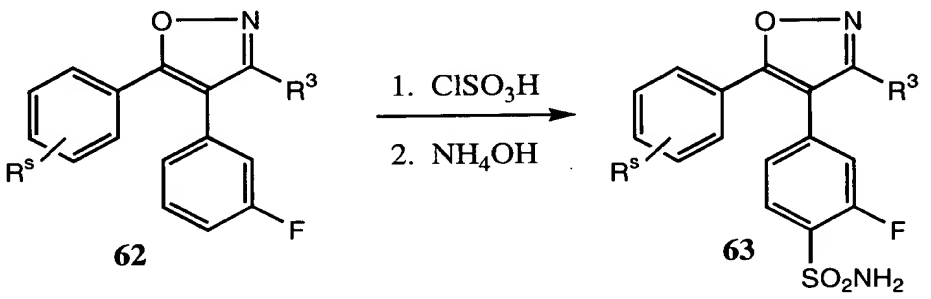
The methylsulfide moeity **58** prepared in **Scheme XXIV** can be converted to the sulfonamide or methylsulfone diarylisoxazole **59** as previously described.

Scheme XXVI



Scheme XXVI illustrates a three step procedure for the preparation of another isoxazole isomer. In step one, substituted 1,2-diphenylbutenone **60** is converted to the oxime **61** by treatment with hydroxylamine hydrochloride in the presence of sodium acetate in aqueous ethanol. The oxime **61** is then reacted with potassium iodide and iodine in the presence of base, such as sodium bicarbonate to afford a halo intermediate. Sodium bisulfite is added to form the isoxazole **62**.

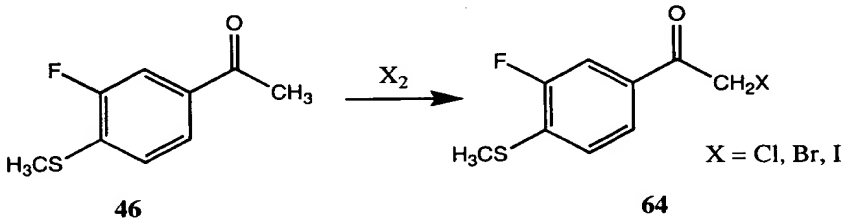
Scheme XXVII



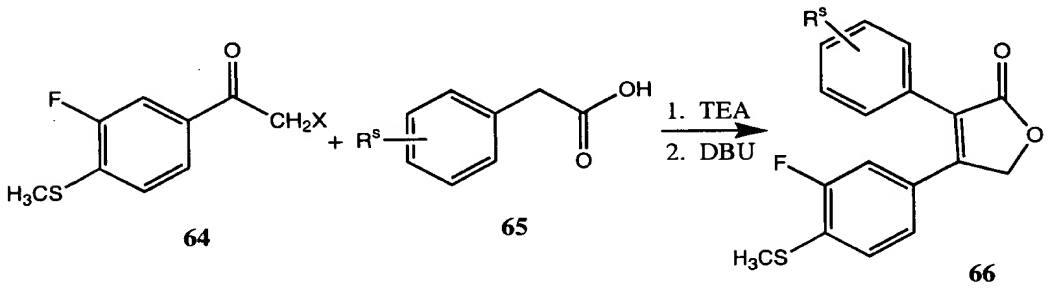
62 63

Treatment of the isoxazole **62** with chlorosulfonic acid provides, after workup, the intermediate sulfonyl chloride which can be converted to the sulfonamide **63** by mixing with ammonia in various solvents. In addition, diaryl/heteroaryl isoxazoles comprising the 3-fluoro-4-sulfonamidyl-phenyl moiety can be prepared in accordance with the methods described in PCT Application Serial No. US96/01869, PCT documents WO92/05162 and WO92/19604, and European Publication EP 26928, which are incorporated by reference.

Scheme XXVIII



46 64

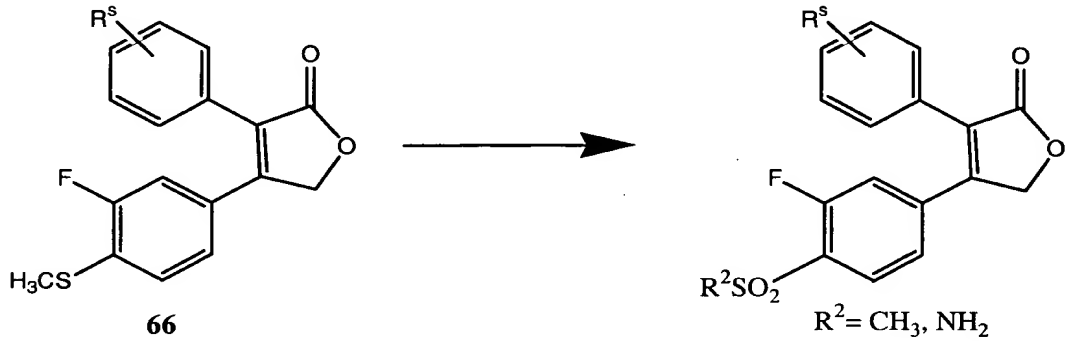


64 65 66

Scheme XXVIII illustrates a synthetic pathway for preparation of furanones. The acetophenone **46** is halogenated in acetic acid to afford the acylhalide **64**. Displacement of the halide **64** with phenylacetic acid **65** in the presence of triethylamine in acetonitrile

followed by addition of diazobi-cyclo[5.4.0]undec-7-ene affords the furanone **66** [Ahluwalia, *Synth. Commun.* **19**, 619-626 (1989)].

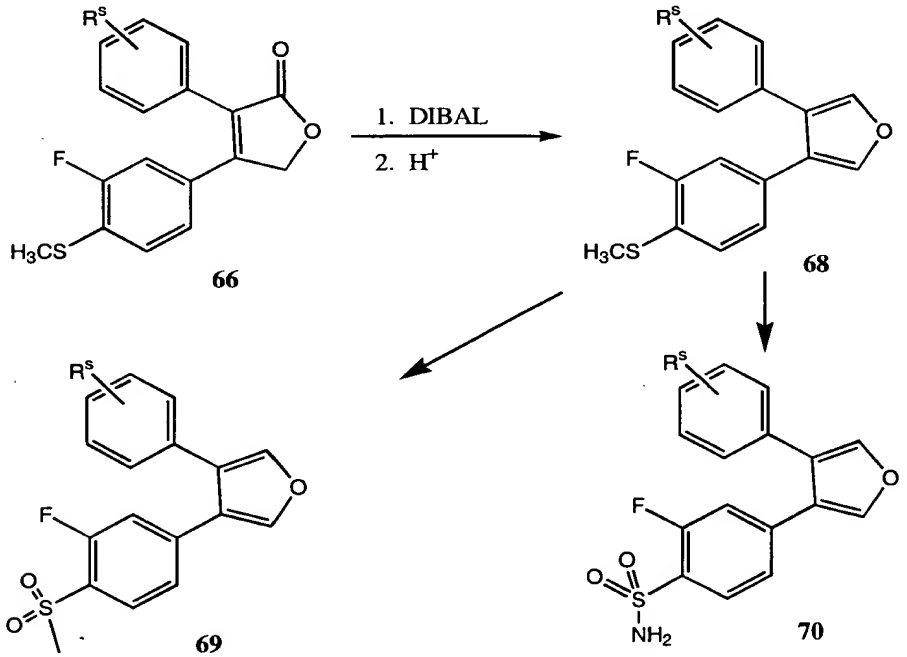
Scheme XXIX



66 **67**

The methylthiofuranone **66** can be converted to the methylsulfonyl or sulfoamide furanone **67** as previously disclosed.

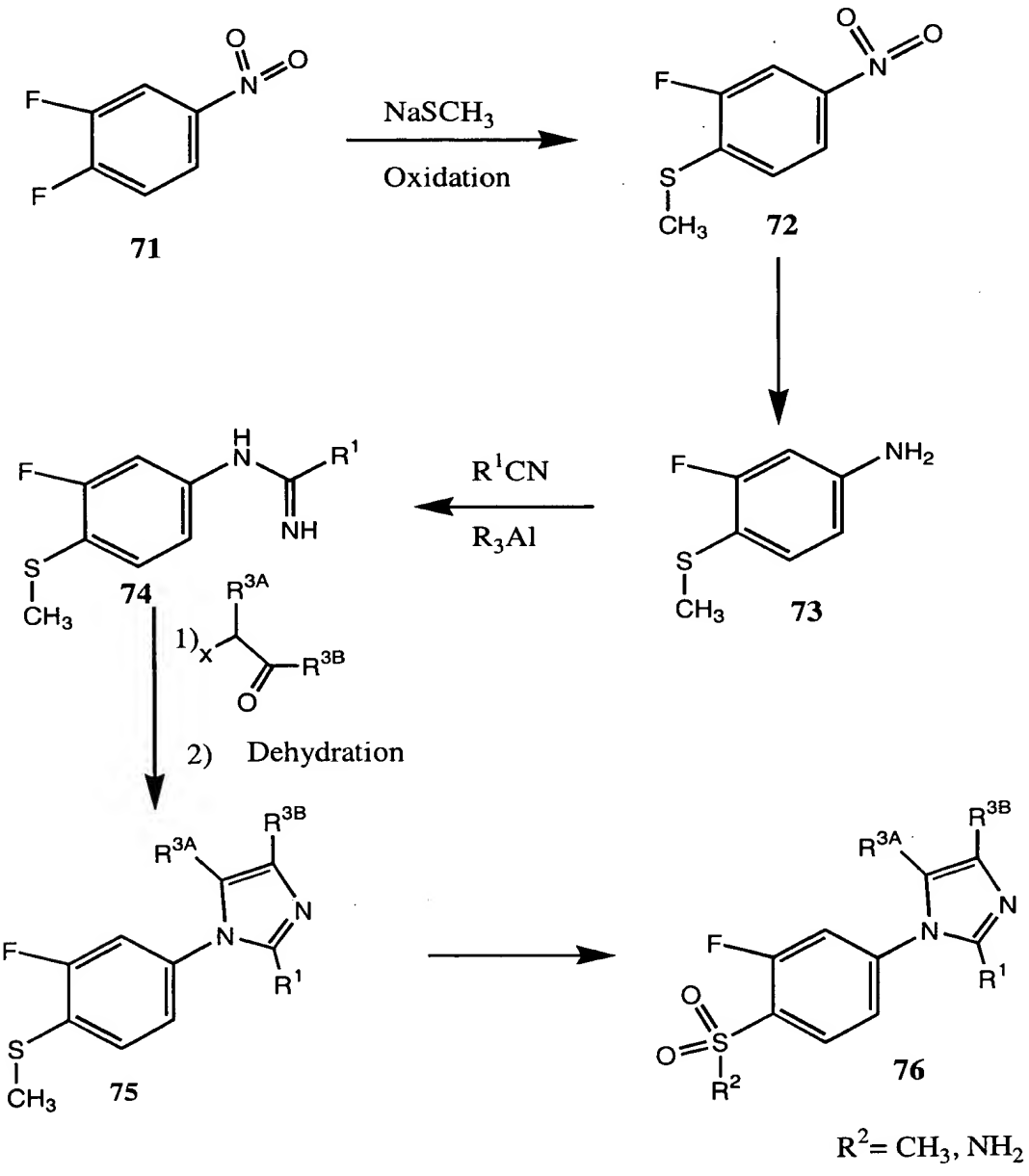
Scheme XXX



66 **68** **69** **70**

The furan **68** can be prepared from the furanone **66** by reduction and rearomatization though dehydration. Treatment of the furanone **66** in chlorinated solvents such as dichloromethane at reduced temperatures with hydride reagents such as diisobutylaluminum hydride (DIBAL-H) followed by treatment with mineral acids to catalyze the dehydration of the resulting hemiacetal affords the furan **68** [Singh, *Indian J Chem, Sect B.*, **29**, 954-960 (1990)]. The sulfide can be converted to the sulfone **69** and sulfonamide **70** as previously described.

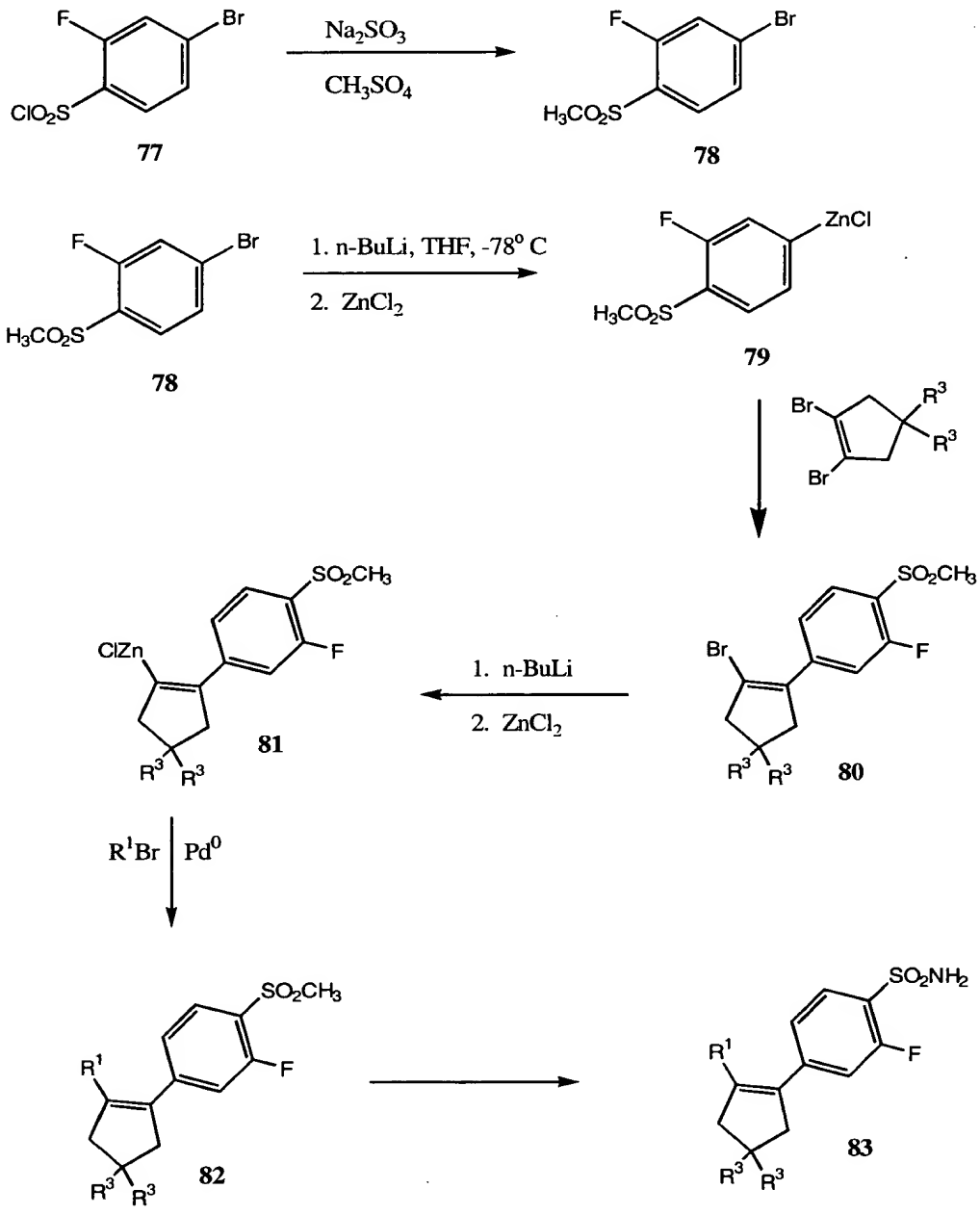
Scheme XXXI



Scheme XXXI illustrates the preparation of the substituted diarylimidazole **76** which comprises a 3-fluoro-4-sulfonylphenyl moiety. Substitution of the 4-fluorine in 3,4-difluoro-nitrobenzene **71** with sodium thiomethoxide provides the 3-fluoro-4-methylthio-nitrobenzene **72**. Reduction of the nitro group to an amine can be accomplished through hydrogenation over a metallic catalyst such as palladium or platinum on various supports. The resulting phenylamine **73** can be reacted with a substituted nitrile in the presence of alkylaluminum reagents such as trimethylaluminum in inert solvents such as toluene or benzene affording amidine **74**. Mixing of the amidine **74** with a 2-haloketone in the presence of mild inorganic or organic bases such as triethylamine, diisopropylamine, or sodium bicarbonate in solvents such as acetone, acetonitrile, or dimethylformamide gives a 4,5-dihydroimidazole that can be dehydrated in the presence of catalytic mineral acids to afford the 1,2-disubstituted imidazole **75**.

These types of diaryl/heteroaryl imidazoles also can be prepared in accordance with the methods described in U.S. Patent Nos. 4,822,805 and PCT documents WO 93/14082 and WO96/03388, which are incorporated by reference. The methylsulfide then can be converted to the sulfone or sulfonamide affording substituted diarylimidazole **76** as previously described.

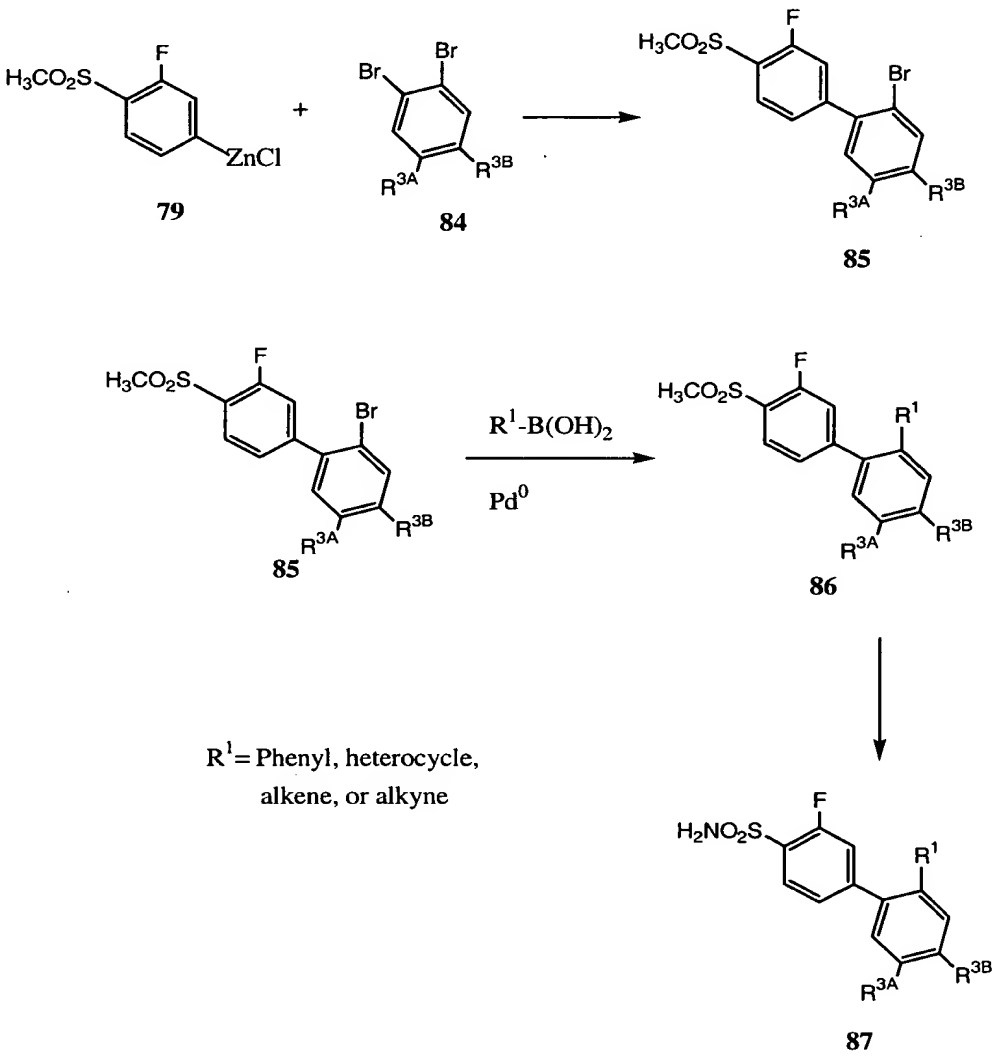
Scheme XXXII



The commercially available 4-bromo-2-fluorobenzenesufonyl chloride **77** can be treated with sodium sulfite followed by treatment with dimethylsulfate to afford the 4-bromo-2-fluoromethylsulfonyl-benzene **78** [Organic Synthesis, **Volume IV** page 674]. Diaryl/heteroaryl cyclopentene **82** comprising the orthofluorosulfonyl functional group can be prepared from the 4-bromo-2-fluoromethylsulfonyl-benzene **78** as described in **Scheme XXXII** in accordance with the methods described in U.S. Patent No 5,344,991 and PCT

document WO 95/00501, which are incorporated by reference. The sulfone can be converted to the cyclopentenphenylsufonamide **83** as described previously.

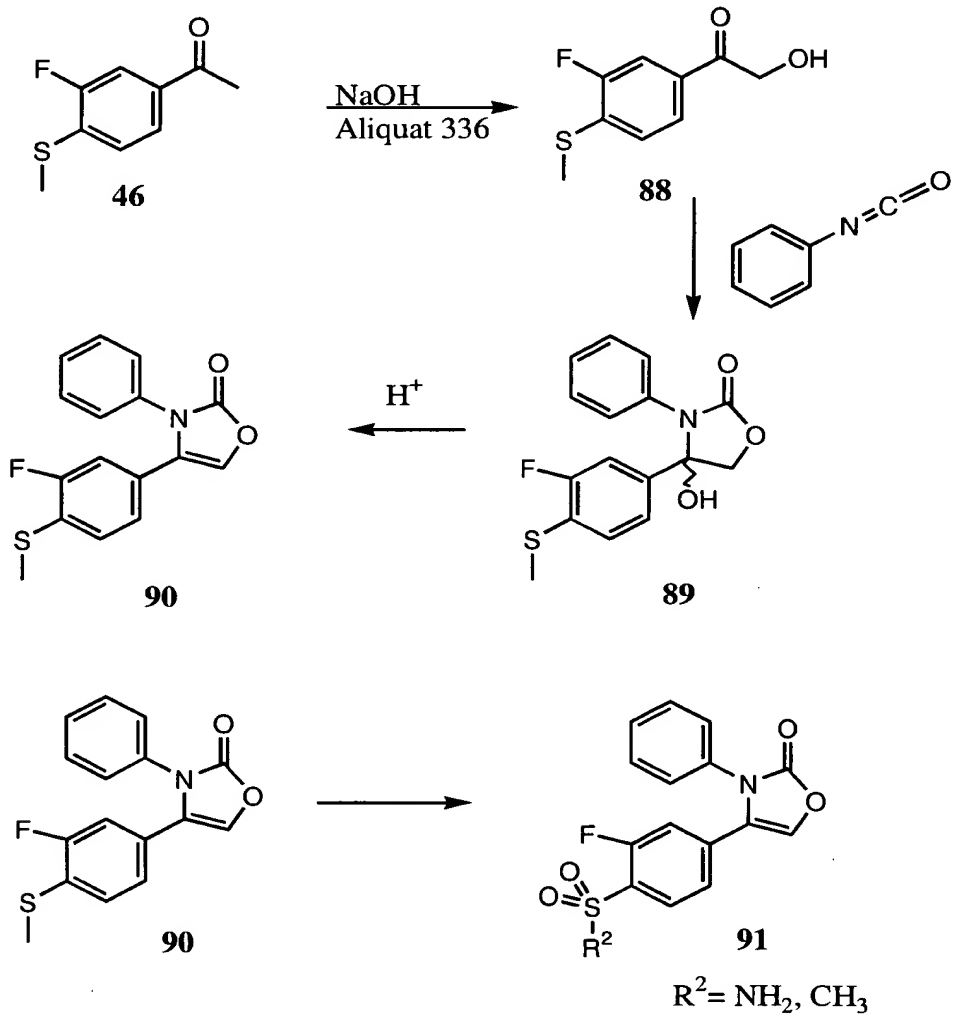
Scheme XXXIII



Scheme XXXIII similarly illustrates a procedure for the preparation of 1,2 diarylbenzene **87** comprising the orthofluorosulfonyl functional group from bromo-biphenyl intermediate **86** using the appropriate substituted phenyl boronic acid in a Suzuki coupling procedure [Synth. Commun., **11**, 513 (1981)]. Bromo-biphenyl intermediate **86** can be prepared in a manner similar to the procedure described in Scheme **XXXII.**

Sulfonamides can be prepared from the sulfones as described earlier in this application. U.S. Application Serial No. 08/346,533 generally describes the preparation of terphenyl coumpounds and is incorporated by reference.

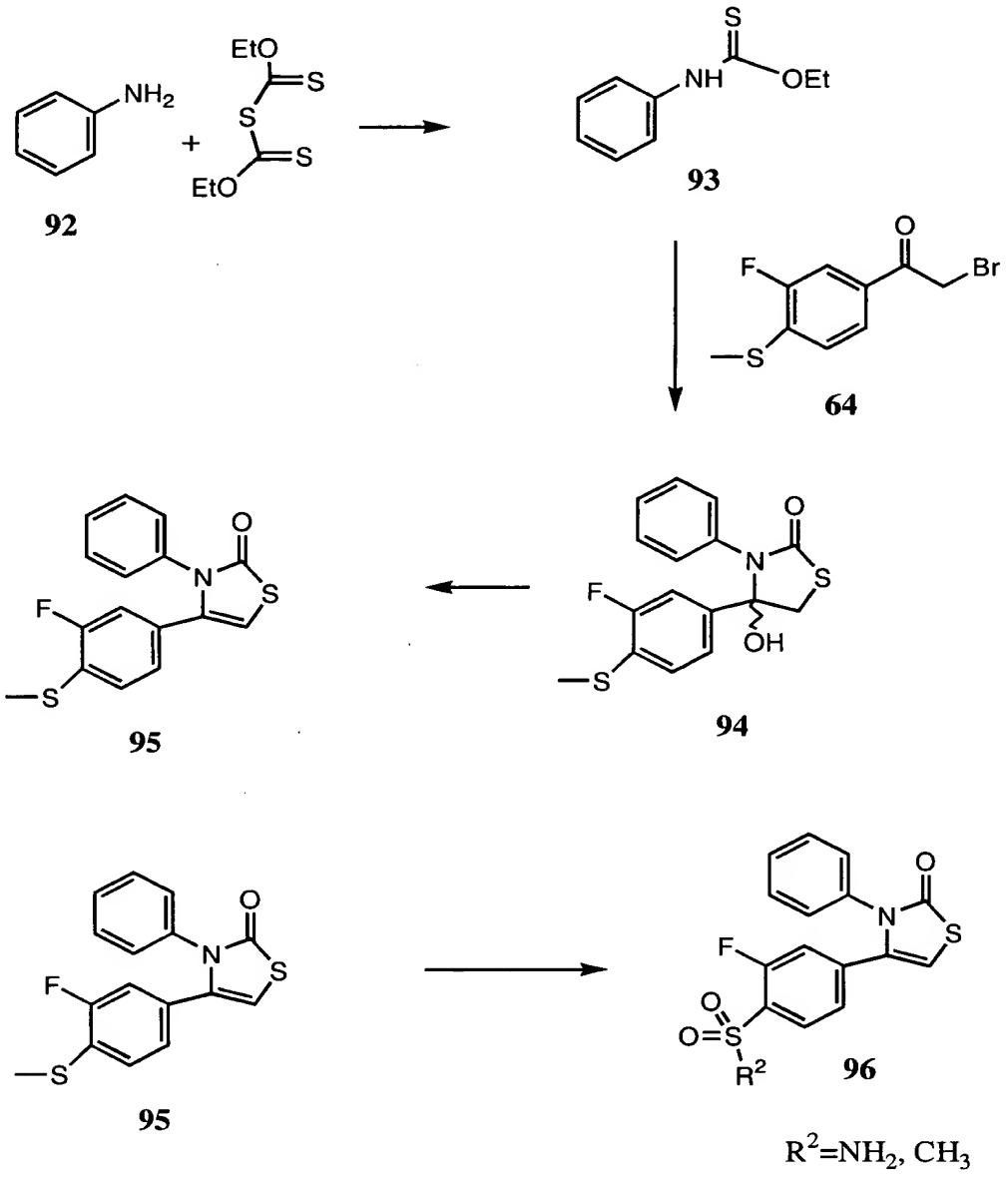
Scheme XXXIV



Scheme **XXXIV** illustrates the preparation of the 3,4-diaryloxazol-2-one **91** and its derivatives. Oxidation of the methyl group adjacent to the carbonyl carbon of the 3-fluoro-4-methyl-sulfonylacetophenone **46** to an alcohol can be accomplished using base, aliquat 336 and oxygen (see, e.g., EP 197704). Treatment of the resulting alcohol **88** with an

isocynate followed by dehydration of the hydroxy intermediate **89** in the presence of acid affords the oxazolone **90**. The methylsulfide of the oxazolone **90** can be converted to the sulfone or sulfonamide affording substituted 3,4 diaryloxazol-2-ones **91** as previously described. Other 3,4-diaryloxazol-2-one compounds with the basic structure of substituted 3,4 diaryloxazol-2-one **91** that comprise an orthofluorosulfonyl functional group can be prepared starting from the 2-hydroxy-1'-[3'-flouoro-4-methylsulifidophenyl]-ethanone **88** in accordance with the methods described in PCT documents WO 98/11080 and WO 99/14205, which are incorporated by reference.

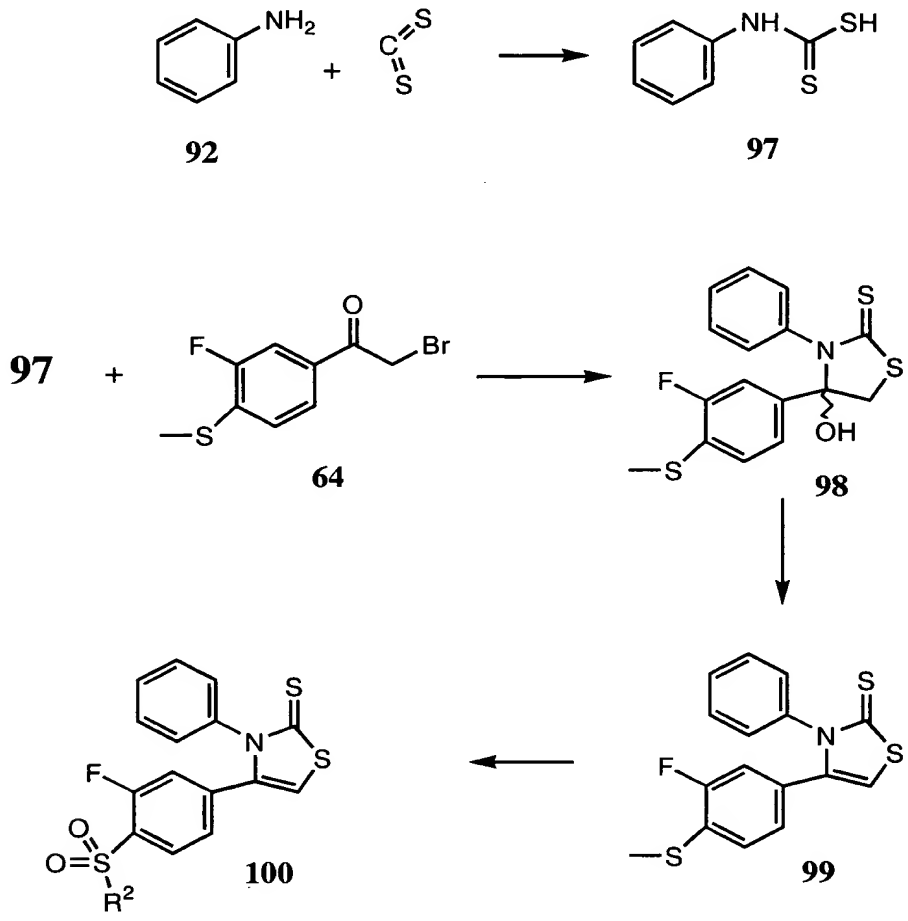
Scheme XXXV



Scheme XXXV illustrates the preparation of 3,4-diarylthiazonlin-2-one. Mixing the analine **92** with bis(ethoxythiocarbonyl) in an alcoholic solvent affords the ethyl-thiocarbamate **93**. Refluxing of ethyl-thiocarbamate **93** and the 2-bromoacetophenone **64** in an ethereal solvent provides the hydroxy intermediate **94**. Heating of the hydroxy intermediate **94** with mineral acids in alcoholic solvents yields the desired 3,4 diarylthiazolin-2-one **95**. U.S. Patent 5,859,036 describes an alternative procedure that can be appropriately modified and used to prepare the compounds. U.S. Patent 5,859,036 is

incorporated by reference. The methyl-sulfide **95** can be converted to the corresponding sulfone or sulfonamide affording substituted 3,4 diarylthiazonlin-2-one **96** as previously described.

Scheme XXXVI



R^2=NH_2, CH_3

Scheme XXXVI illustrates the preparation of 3,4-diarylthiazonlin-2-thione **100**. Mixing of analine **92** with carbon disulfide in an alcoholic solvent affords the dithiocarbamate **97**. Refluxing of dithiocarbamate **97** and the 2-bromoacetophenone **64** in an ethereal solvent provides the hydroxy intermediate **98**. Heating of the hydroxy intermediate **98** with mineral acids in alcoholic solvents yields the desired 3,4 diarylthiazonlin-2-thione **99**. U.S. Patent 5,859,036 illustrates a similar process and is

incorporated by reference. The methylsulfide **99** can be converted to the corresponding sulfone or sulfonamide affording substituted 3,4 diarylthiazonlin-2-thione **100** as previously described.

Working Examples

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulae I-VII. These detailed descriptions fall within the scope, and serve to exemplify, the above-described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

The following abbreviations are used:

HCl - hydrochloric acid

DMSO - dimethylsulfoxide

DMSOd_6 - deuterated dimethylsulfoxide

$CDCl_3$ - deuterated chloroform

$MgSO_4$ - magnesium sulfate

$NaHCO_3$ - sodium bicarbonate

$KHSO_4$ - potassium hydrogen sulfate

DMF - dimethylformamide

NaOH - sodium hydroxide

BOC - *tert*-butyloxycarbonyl

CD_3OD - deuterated methanol

EtOH - ethanol

LiOH - lithium hydroxide

CH_2Cl_2 - methylene chloride

h - hour

hr - hour

min - minutes

THF - tetrahydrofuran

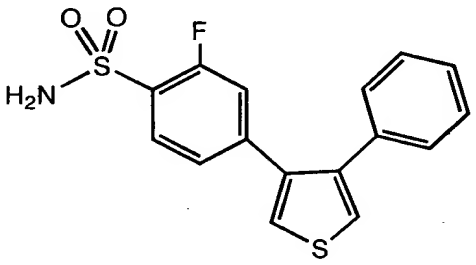
TLC - thin layer chromatography

Et_3N - triethylamine

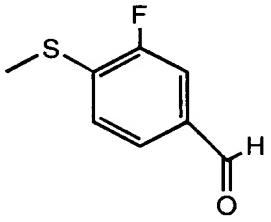
DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

DMAP - 4-dimethylaminopyridine

Example 1



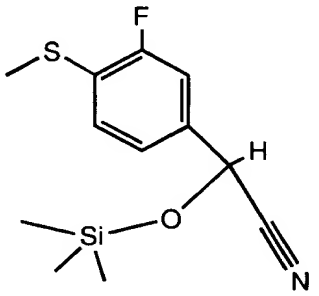
2-Fluoro-4-(4-phenyl-3-thienyl)benzenesulfonamide



Step 1: Preparation of 3-Fluoro-4-(methylthio)-benzaldehyde

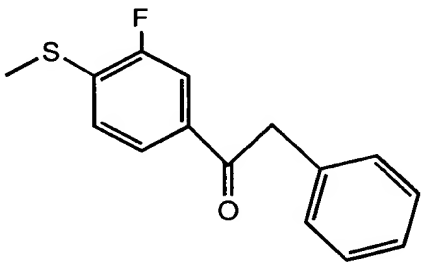
The 3,4-difluorobenzaldehyde (52.1 g, 0.36 mol) was dissolved in acetonitrile (500 mL). Sodium thiomethoxide (25.6 g, 0.36 mol) was added in four equal portions at 15 minute intervals. The slightly exothermic reaction was stirred at room temperature for 4 hours. The reaction mixture was poured into ethyl acetate (500 mL) and extracted with saturated sodium bicarbonate (2 x 200 mL) followed by saturated ammounium chloride (2 x 100 mL). The solution was dried over sodium sulfate and solvent removed at reduced pressure. The 3-fluoro-4-(methylthio)-benzaldehyde (38.5 g, 0.22 mol) was isolated by

vacuum distillation (135-145 °C at 25 mm Hg) as clear liquid. (61% yield) ESHRMS *m/z* 171.0302 (calcd for M+H, 171.0280).



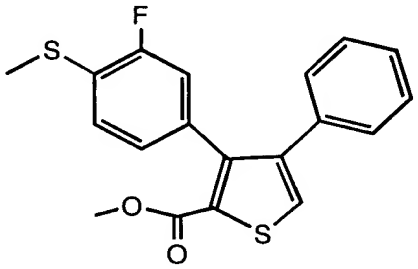
Step 2: Preparation of 3-fluoro-4-(methylthio)-□-[(trimethysilyl)oxy]-benzeneacetonitrile

The 3-fluoro-4-methylthiobenzaldehyde (33.0 g, 194.0 mmol), trimethylsilyl cyanide (19.8 g, 200 mmol) were mixed together in dichloromethane (350 mL) and zinc iodide (35 mg) was addded. The solution was heated to 35 °C. The bath was removed and the solution stirred for 1 hour during which an exotherm was noted. After cooling to room temperature the solvent was removed at reduced pressure to afford the 3-fluoro-4-(methylthio)-□-[(trimethylsilyl)oxy] benzene-acetonitrile (51.6 g, 192 mmol) as a yellow oil. (98 % yield): ^{1}H NMR ($CHCl_3$/300 MHz) 7.24-7.29 (m, 3H), 5.48 (s, 1H), 2.51 (s, 3H), 0.27 (s, 9H). ESHRMS *m/z* 261.0769 (calcd for M+H, 261.0749).



Step 3: Preparation of 1-[3-fluoro-4-(methylthio)-phenyl]-2-phenylethanone

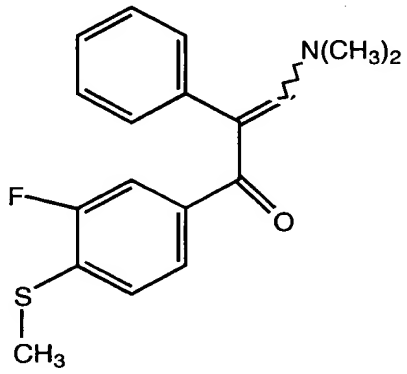
The 3-fluoro-4-(methylthio)-a-[(trimethylsilyl)-oxy]-benzeneacetonitrile (40.1 g, 149 mmol) was cooled to -78 °C in tetrahydrofuran (400 mL). Lithium hexamethydisilazide (175 mL of 1.0 M in Hexanes, 175 mmol) was added drop-wise over 1 hour. The solution was stirred for 1 additional hour at -78 °C. Benzylbromide (24.5 g 149 mmol) was added as a solution in tetrahydrofuran (100 mL) over 25 minutes. The solution was kept at - 78 °C for 1 hour, warmed to room temperature, and kept at room temperature for six hours. The solution was poured into ethyl acetate (300 mL). Aqueous 1 N hydrochloric acid (200 mL) was added and the solution stirred for 48 hours at room temperature. The layers were separated and the organic layer collected. The organic layer was mixed with aqueous 15% sodium hydroxide and stirred for 30 minutes. The organic layer was collected washed with saturated ammounium chloride(200 mL) and solution was dried over sodium sulfate and solvent removed at reduced pressure to afford a yellow oil. The product was isolated by preparative silica chromatography followed by crystallization from 2% ethyl acetate and hexanes (400 mL). 1-[3-fluoro-4-(methylthio)phenyl]-2-phenylethanone (21.5 grams, 82.0 mmol) was obtained as white crystals. (55 % yield): Mp 77.1 - 77.2 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.77, (dd, 1H, J = 8.0, 1.8 Hz), 7.64 (dd, 1H, J = 10.7, 1.8 Hz), 7.20-7.40 (m, 6H), 4.22 (s, 3H), 2.51 (s, 1H).



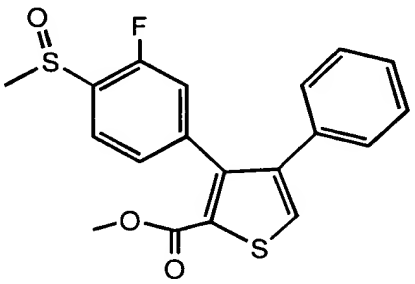
Step 4: Preparation of methyl 3-[3-fluoro-4-(methylthio)phenyl]-4-phenyl-2-thiophenecarboxylate

The 1-[3-fluoro-4-(methylthio)phenyl]-2-phenylethanone (21.9 g, 81.5 mmol) and dimethylacetal of dimethylformamide (41.3 g, 347 mmol) were refluxed in toluene (200 mL) for 16 hours. The yellow solution was cooled to room temperature and solvent removed ad reduced pressure. The resulting yellow oil was dissolved in 50% ethyl

acetate/50% hexanes (200 mL) and vacuum filtered through silica gel. The silica was washed with 50% ethyl acetate/50% hexanes (150 mL). The filtrates were combined and solvent removed at reduced pressure to afford 25.19 g the enamine (shown below) as a yellow oil.

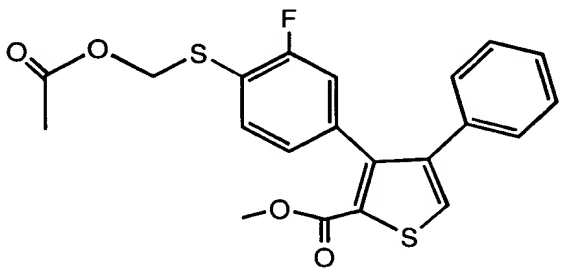


The enamine (25.09 g, 79.3 mmol) and methyl thio-glycolate (35.5 g, 326 mmol) were refluxed for 16 hours. The solvent was removed at reduced pressure and the resulting oil taken up in methanol (300 mL). 25% sodium methoxide in methanol (75.0 mL, 326 mmol) was added and the reaction stirred. After 20 minutes of mixing a precipitate formed and the mixing ceased. The solution was kept at room temperature for 6 hours and the crystals collected. Methyl 3-[3-fluoro-4-(methylthio)phenyl]-4-phenyl-2-thiophenecarboxylate (18.3 grams, 51.7 mmol) was isolated as white crystals. 200 mg of the lot was recrystalized from ethyl acetate and hexanes for analytical data and the remainder used without further purification.(64 % Yield): Mp 140.6-141.0 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.52 (s, 1H), 7.52 (s, 1H), 7.21-7.80 (m, 3H), 7.17 (t, 1H, J = 8.0 Hz),7.06-7.12 (m, 2H), 6.86-6.97 (m, 2H), 3.81(s, 3H), 2.50(s, 3H). ESHRMS *m/z* 359.0598 (calcd for M+H$^+$, 359.0576)



Step 5: Preparation of methyl 3-[3-fluoro-4-(methylsulfinyl)phenyl]-4-phenyl-2-thiophenecarboxylate.

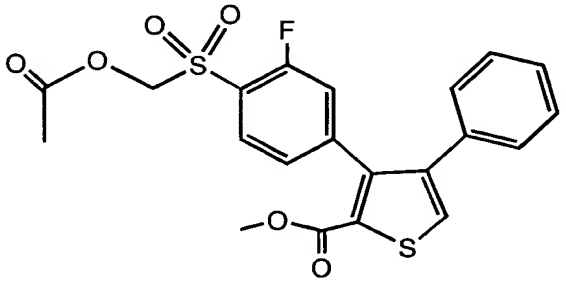
The methyl 3-[3-fluoro-4-(methylthio)phenyl]-4-phenyl-2-thiophenecarboxylate (5.00 g, 13.9 mmol) was dissolved in dichloromethane (100 mL) and methanol (30 mL). Magnesium monoperoxyphathalate hexahydrate (MMPP)(3.78 g of 80%, 7.6 mmol) was added in five equal portions at 1 minute intervals. The resulting heterogeneous solution was stirred for 1 hour. Additional MMPP (600 mg, 1.6 mmol) was added and the solution stirred for 15 min. The reaction was complete and solution extracted with saturated sodium bicarbonate (2 x 100 mL). The organic layer was dried over sodium sulfate and solvent removed at reduced pressure. Methyl 3-[3-fluoro-4-(methylsulfinyl)phenyl]-4-phenyl-2-thiophenecarboxylate was isolated by crystallization from dichloromethane and hexanes. (81% yield): Mp 164.0-164.1 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.75 (t, 1H, J = 7.7 Hz), 7.53 (s, 1H), 7.15-7.26 (m, 3H), 6.94-7.40 (m, 3H), 3.90 (s, 3H), 2.85 (s, 3H). ESHRMS *m/z* 375.0536 (calcd for M+H, 375.0525).



Step 6: Preparation of methyl 3-[4-[[(acetyloxy)-methyl]thio]-3-fluorophenyl]-4-phenyl-2-thiophenecarboxylate

The methyl 3-[3-fluoro-4-(methylsulfinyl)phenyl]-4-phenyl-2-thiophenecarboxylate (4.13 g, 11.04 mmol) was dissolved in acetic anhydride (45.0 mL). Powdered sodium acetate (4.0 g, 48.7 mmol) was added and the solution was refluxed for 8 hours. The solution was poured into a 500 mL round bottom flask and solvent removed at reduced pressure. The residue was take up in ethyl acetate (200 ml) and dichloromethane (20 mL).

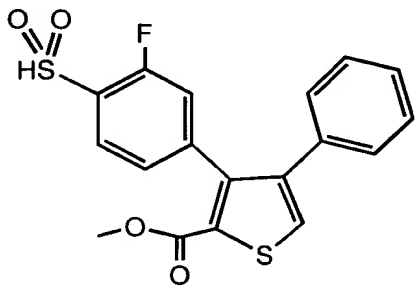
The solution was extracted with saturated sodium bicarbonate (3 x 100 mL) followed by saturated ammonium chloride (2 x 100 mL). The solvent was removed at reduce pressure and residue taken up in ether, dried over sodium sulfate and solvent removed at reduced pressure. Methyl 3-[4-[[(acetyloxy)methyl]thio]-3-fluorophenyl]-4-phenyl-2-thiophenecarboxylate (2.9 g, 6.90 mmol) was isolated by crystallization from diethyl ether and hexanes as white crystals. (62 % yield). Mp 102.9-103.7 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.53 (s, 1H), 7.43 (t, 1H, J = 7.8 Hz), 7.22-7.28 (m, 3H), 7.04-7.08 (m, 2H), 6.92-6.98 (m, 2H), 5.42 (s, 2H), 3.81 (s, 3H), 2.11 (s, 3H). ESHRMS *m/z* 434.0898 (calcd for M+NH_4^+, 434.0896)



Step 7: Preparation of methyl 3-[4-[[(acetyloxy)methyl]-sulfonyl]3-fluorophenyl]-4-phenyl-2-thiophenecarboxylate

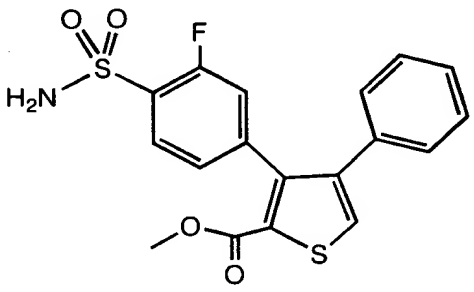
The methyl 3-[4-[[(acetyloxy)methyl]thio]-3-fluorophenyl]-4-phenyl-2-thiophenecarboxylate (3.56 g, 8.55 mmol), MMPP (5.80g of 80%, 9.45 mmol) were mixed in methanol (30 mL) and dichloromethane (100 mL). The solution was mixed at room temperature for 16 h and additional MMPP (2.00 g) was added. The solution was heated to reflux for 8 hours. The solution was poured into ethyl acetate (200 mL) and extracted with saturated aqueous sodium bicarbonate (2 x 100 mL) followed by brine (100 mL). The organic layer was collected and solvent removed at reduced pressure. The resulting white semi-solid was triturated with ethyl acetate and hexanes. Methyl 3-[4-[[(acetyloxy)methyl]-sulfonyl]3-fluorophenyl]-4-phenyl-2-thiophene-carboxylate (3.15 g, 7.03 mmol) was isolated as an off white solid. (82 % yield). Mp 164.7-164.8 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.82 (t, 1H, J = 7.5 Hz), 7.56 (s, 1H), 7.22 - 7.30 (m, 2H), 7.13 (d, 2H, J = 9.2 Hz),

7.00-7.67 (m, 2H), 5,35 (s, 2H), 3.82 (s, 3H), 2.09 (s, 3H). ESHRMS *m/z* 466.0796 (calcd for $M+NH_4^+$, 466.0794)



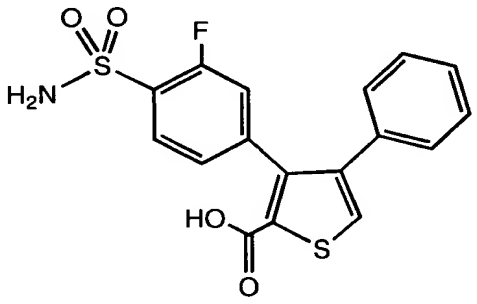
Step 8: Preparation of 2-methyl 3-(3-fluoro-4-sulfinophenyl)-4-phenyl-2-thiophenecarboxylate

The methyl 3-[4-[[(acetyloxy)methyl]sulfonyl]3-fluorophenyl]-4-phenyl-2-thiophenecarboxylate (2.75 g, 6.13 mmol) was dissolved in tetrahydrofuran (100 mL) and stirred at room temperature. 25% Sodium methoxide in methanol (3.0 mL) was added and the solution stirred for 5 min. The resulting slurry was poured into ethyl acetate (200 mL) and aqueous 1N hydrochloric acid (100 mL) was added. The solution was stirred and the layers allowed to separate. The organic layer was collected and the aqueous layer back extracted with ethyl acetate (100 mL). The organic layers were combined, extracted with brine, dried over sodium sulfate, and solvent removed at reduced pressure. The 2-methyl 3-(3-fluoro-4-sulfinophenyl)-4-phenyl-2-thiophenecarboxylate (1.87 g, 4.59 mmol) was isolated as a white solid.(77 % yield). Mp 132.6-133.1 °C ^{1}H NMR ($CDCl_3$/300 MHz) 7.74-7.80 (1H, m), 7.55 (s, 1H), 6.80-7.28 (m, 6H), 3,74 (s, 3H). ESHRMS *m/z* 394.0586 (calcd for $M+NH_4^+$, 394.0583)



Step 9: Preparation of methyl 3-[3-fluoro-4-(sulfonamido)phenyl]-4-phenyl-2-thiophenecarboxylate

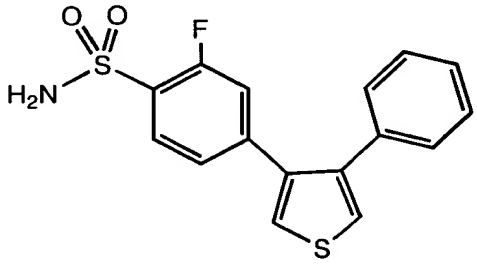
The 2-methyl 3-(3-fluoro-4-sulfinophenyl)-4-phenyl-2-thiophenecarboxylate (1.51 g, 4.01 mmol) was dissolved in methanol (25 mL). Water (10 mL) was added and the solution became slightly clouldy. Sodium acetate (2.62 g, 32.0 mmol) and hydroxyamine-O-sulfonic acid (1.80 g, 16.6 mmol) were mixed toeghter at room temperature for 4 Hours. The solution was poured into ethyl acetate (100 mL) and extracted with 1N aqueous hydrochloric acid (2 X 50 mL), water (2 X 50 mL), saturated sodium bicarbonate (2 x 50 mL) and brine (50 mL). The solution was dried over anhydrous sodium sulfate and solvent removed at reduced pressure. The methyl 3-[3-fluoro-4-(sulfonamido)phenyl]-4-phenyl-2-thiophene-carboxylate (1.04 g, 2.65 mmol) was isolated as a white solid by crystallizations from ethyl acetate and hexanes. (66 % yield). Mp 168.3-168.4 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.78 (t, 1H, J = 7.6 Hz), 7.51 (s, 1H), 7.20-7.61 (m, 3H), 6.80-7.10 (m, 4H), 5.01 (bs, 2H), 3.77 (s, 3H). ESHRMS *m/z* 409.0684 (calcd for M+NH_4^+, 409.0692)



Step 10: Preparation of 3-[3-fluoro-4-(sulfonamido)-phenyl]-4-phenyl-2-thiophenecarboxylic acid.

The methyl 3-[3-fluoro-4-(sulfonamido)phenyl]-4-phenyl-2-thiophene-carboxylate (922 mg, 2.35 mmol) and lithium hydroxide (356 mg, 8.00 mmol) were mixed in tetra-hydrofuran (14.0 mL), methanol (4.0 mL), and water (2.0 mL) at room temperature for 16 hours. The solution was poured into ethyl acetate (100 mL) and extracted with 1 N hydrochloric acid (2 x 50 mL) followed by brine (50 mL). The solution was dried over sodium sulfate and solvent removed at reduced pressure. The 3-[3-fluoro-4-(sulfonamido)-

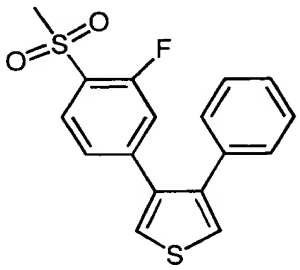
phenyl]-4-phenyl-2-thiophenecarboxylic acid (723 mg, 2.14 mmol) was isolated as a white solid by crystallization from ethyl acetate and hexanes.(91 % yield). Mp 214.6-214.7 °C. ^{1}H NMR (DMSOd_6/400 MHz) 13.2 (bs, 1H), 7.92 (s, 1H), 7.66 (bs, 2H), 7.60 (t, 1H, J = 7.9 Hz), 7.20-7.28 (m, 4H), 7.00-7.60 (m, 3H). ESHRMS *m/z* 395.0522 (calcd for M+NH_4^+, 395.0536)



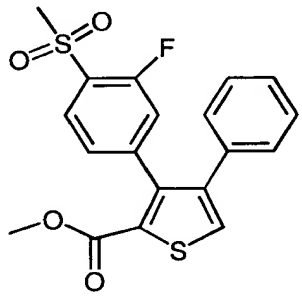
Step 11: Preparation of 2-fluoro-4-(4-phenyl-3-thienyl)benzenesulfonamide

The 3-[3-fluoro-4-(sulfonamido)-phenyl]-4-phenyl-2-thiophenecarboxylic acid (331 mg, 0.87 mmol) and copper powder (150 mg) were heated in freshly distilled quinoline (15 mL) to 160 °C for 1 hour. The reaction was cooled to room temperature and poured into ethyl acetate (100 mL). The solution was extracted to with 1N hydrochroic acid (2 x 100 mL), saturated sodium bicarbonate (2 x 100 mL) and brine (100 mL). The solution was dried over sodium sulfate and solvent removed at reduced pressure. The thiophene (113 mg, 0.34 mmol) was isolated as a white solid by flash chromatography (ethyl acetate/ hexanes) followed by crystallization from hot diethyl ether and hexanes. (38 % yield).Mp 170.9-171.0 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.79 (t, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 3.22 Hz), 7.38 (d, 1H, *J* = 3.22 Hz), 7.32-7.60 (m, 3H), 7.18-7.22 (m 2H), 7.40-7.12 (m, 2H), 5.03 (bs, 2H). ESHRMS *m/z* 351.0647 (calcd for M+NH_4^+, 351.0367).

Example 2



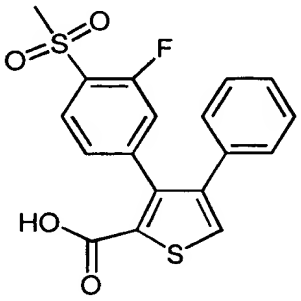
3-[3-Fluoro-4-(methylsulfonyl)phenyl]-4-phenylthiophene



Step 1: Preparation of methyl 3-[3-fluoro-4-(methylsulfonyl)phenyl]-4-phenyl-2-thiophenecarboxylate

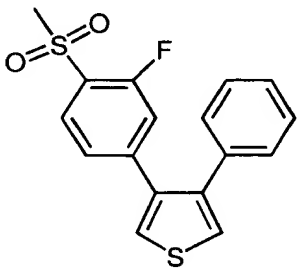
Methyl 3-[3-fluoro-4-(methylthio)phenyl]-4-phenyl-2-thiophenecarboxylate (5.15 g, 14 mmol, from example 1 step 4) was dissolved in dichlormethane (100 mL) and methanol (30 mL). Magnesium monoperoxyphathalate hexahydrate (MMPP)(10.25 g of 80%, 17 mmol) was added in five equal portions at 1 minute intervals. The resulting heterogeneous solution was stirred overnight at ambient temperature. Ethyl acetate (200 mL) was added and the solution extracted with saturated sodium bicarbonate (2 x 100 mL). The organic layer was dried over sodium sulfate and solvent removed *in vacuo*. Methyl 3-[3-fluoro-4-(methylsulfonyl)phenyl]-4-phenyl-2-thiophenecarboxylate (5.27 g, 12.9 mmol)was isolated by crystallization from ethyl acetate and hexanes (92 % Yield): mp 181-182 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.87 (t, 1H, J = 7.7 Hz), 7.56 (s, 1H), 7.26-7.24 (m, 4H), 7.15 (s, 1H), 7.12-7.10 (m, 1H), 7.04-7.01 (m, 2H), 3.83 (s, 3H), 3.26 (s, 3H). ESHRMS *m/z* 408.0738

(M+H$^+$, Calcd 408.0740). Anal. Calcd for $C_{19}H_{15}FO_4S_2$: C, 58.45; H, 3.87; Found: C, 58.22; H, 3.78.



Step 2: Preparation of 3-[3-fluoro-4-(methylsulfonyl-phenyl-4-phenyl-2-thiophenecarboxylic acid

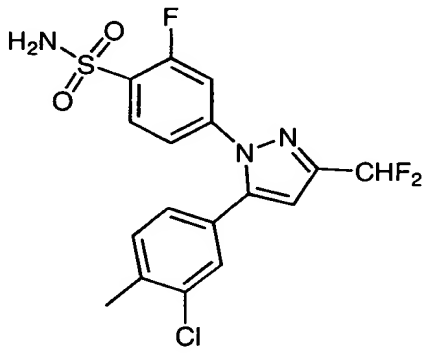
Methyl 3-[3-fluoro-4-(methylsulfonyl)phenyl]-4-phenyl-2-thiophenecarboxylate (2.46 g, 63 mmol) was dissolved in tetrahydrofuran (25 mL), methanol (175 mL) and water (50 mL). Lithium hydroxide (0.66 g, 157 mmol) was added and the mixture was stirred overnight at ambient temperature. The organic solvents were removed *in vacuo* and the aqueous suspension was poured into ethyl acetate (100 mL). The solution was extracted with 10% aqueous hydrochloric acid (2 X 100 mL), water (2 X 100 mL), saturated ammonium chloride (2 X 100 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* and 3-[3-fluoro-4-(methylsulfonylphenyl-4-phenyl-2-thiophenecarboxylic acid(2.12 g, 56.0 mmol) was obtained by crystallization from ethyl acetate and hexanes (90 % yield): mp 216-218 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.86 (t, 1H, J = 7.7 Hz), 7.65 (s, 1H), 7.29-7.26 (m, 3H), 7.14-7.11 (m, 2H), 7.04-7.00 (m, 2H), 3.28 (s, 3H). ESHRMS *m/z* 394.0539 (M+NH_4^+, Calcd 394.0583). Anal. Calcd for $C_{18}H_{13}FO_4S_2$: C, 57.43; H, 3.48; Found: C, 56.94; H, 3.41.



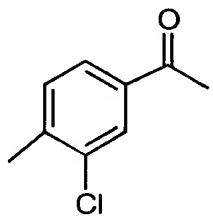
Step 3: Preparation of 3-[3-fluoro-4-(methylsulfonyl)-phenyl]-4-phenylthiophene

3-[3-Fluoro-4-(methylsulfonylphenyl-4-phenyl-2-thiophenecarboxylic acid (1.02 g, 3 mmol) was dissolved in freshly distilled quinoline (10 mL) and powdered copper (0.09 g, 1.3 mmol) was added. The reaction was heated to 130 °C for 3 hours. The reaction was cooled to ambient temperature and poured into aqueous 10% hydrochloric acid (50 mL) and ethyl acetate (50 mL). The solution was extracted with 10% aqueous hydrochloric acid (2 X 50 mL), water (2 X 50 mL), saturated ammonium chloride (2 X 50 mL) and dried over sodium sulfate. 3-[3-Fluoro-4-(methylsulfonyl)phenyl]-4-phenylthiophene (0.55 g, 1.60 mmol) was isolated by preparative silica chromatography followed by crystallization from ethyl acetate and hexanes (54 % yield): mp 140-141 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.84 (t, 1H, J = 7.9 Hz), 7.43 (ab, 2H, J = 13.79 Hz, $\Delta\nu$ = 27.28), 7.35-7.33 (m, 3H), 7.21-7.07 (m, 4H), 3.25 (s, 3H). ESHRMS *m/z* 350.0686 ($M+NH_4^+$, Calcd 350.0685). Anal. Calcd for $C_{17}H_{13}FO_2S_2$: C, 61.42; H, 3.94; Found: C, 61.44; H, 3.94.

Example 3

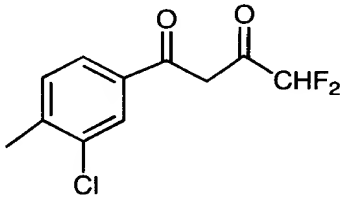


4-[5-(3-chloro-4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide



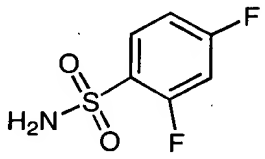
Step 1: Preparation of 1-(3-chloro-4-methylphenyl)-ethanone

3'-Chloro-4'-methylacetophenone (26.8 g, 200 mmol) and aluminum chloride (80.0 g, 600 mmol) were stirred in chloroform (200 mL) at room temperature while chlorine gas (14.2 g, 200 mmol) was added over a half hour period. The reaction was stirred for 2 hours at ambient temperature. The mixture was poured into ice and extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were washed with 10% aqueous hydrochloric acid (2 X 100 mL) and water (2 X 100 mL). The resulting solution was dried over magnesium sulfate and concentrated. 1-(3-chloro-4-methylphenyl)ethanone was purified by distillation from 78-95 °C at 0.1 T and formed a light yellow solid upon standing. This material was used in the next step without further purification or characterization.



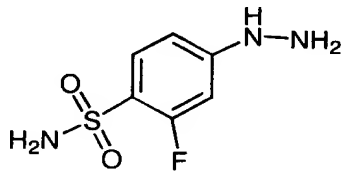
Step 2: Preparation of 1-(3-chloro-4-methylphenyl)-4,4-difluoro-1,3-butanedione

1-(3-chloro-4-methylphenyl)ethanone (7.60 g, 45 mmol), ethyl difluoroacetate (6.20 g, 50 mmol) and sodium methoxide (14 mL) were stirred in diethyl ether (50 mL) at ambient temperature for 5 hours. Ethyl acetate (50 mL) was added to the reaction and it was extracted with 10% aqueous hydrochloric acid (2 X 50 mL), water (2 X 50 mL), saturated ammonium chloride (2 X 50 mL) and dried over sodium sulfate. Solvent was removed *in vacuo* to yield a yellow solid, 1-(3-chloro-4-methylphenyl)-4,4-difluoro-1,3-butanedione (4.95 g, 20.2 mmol, 45 % yield): mp 40-41 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.93 (d, 1H, J = 1.7 Hz), 7.56 (dd, 1H, J = 7.9, 1.7 Hz), 7.37 (d, 1H, J = 7.9 Hz), 6.54 (s, 1H), 6.04 (t, 1H, J = 54.2), 2.48 (s, 3H). ESHRMS m/z 246.0286 ($M+H^+$, Calcd 246.0259). Anal. Calcd for $C_{11}H_9F_2ClO_2$: C, 53.57; H, 3.68; Found: C, 53.10; H, 3.51.



Step 3: Preparation of 2,4-difluorobenzenesulfonamide

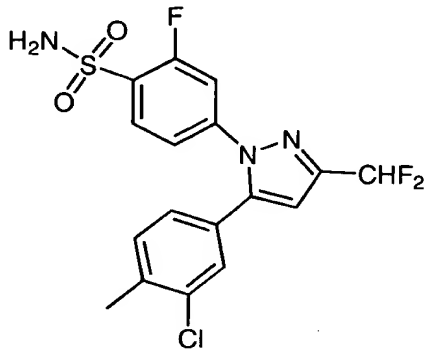
2,4-Difluorobenzenesulphonyl chloride (50.26 g, 237 mmol) was combined with concentrated ammonium hydroxide (100 mL) in methylene chloride (800 mL) and stirred at ambient temperature for 2 hours. Methylene chloride was removed *in vacuo* and solids were dissolved in ethyl acetate (800 mL). The solution was extracted with water (2 X 500 mL), saturated ammonium chloride (2 X 500 mL) and dried over sodium sulfate. The solvent was removed *in vauo* and 2,4-difluorobenzenesulfonamide was obtained by crystallization from ethyl acetate and hexanes (43.27 g, 225 mmol, 95 % yield): mp 155-156 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.46-7.38 (m, 1H), 6.87 (brs, 2H), 6.59-6.51 (m, 2H). ESHRMS *m/z* 192.9990 ($M+H^+$, Calcd 193.0009). Anal. Calcd for $C_6H_5F_2NO_2S$: C, 37.31; H, 2.61; N, 7.25; Found: C, 37.38; H, 2.51, N 7.26.



Step 4: Preparation of 2-fluoro-4-hydrazinobenzene-sulfonamide

2,4-difluorobenzenesulfonamide (23.43 g, 121 mmol) and anhydrous hydrazine (17.00 g, 364 mmol) were refluxed in acetonitrile (300 mL) for two hours. The solvent was removed *in vacuo* and the solid stirred vigorously in ethyl acetate (200 mL) overnight. The solids removed by filtration and discarded and the ethyl acetate was removed *in vacuo* to afford a white solid. 2-Fluoro-4-hydrazinobenzenesulfonamide(6.05 g, 29.5 mmol) was isolated by preparative silica chromatography followed by crystallization from ethyl acetate and hexanes (24 % yield): mp 136-137 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.73 (s, 1H), 7.43 (t, 1H, J = 8.7 Hz), 7.17 (s, 2H), 6.62-6.51 (m, 2H), 4.28 (s, 2H). ESHRMS *m/z* 206.0451

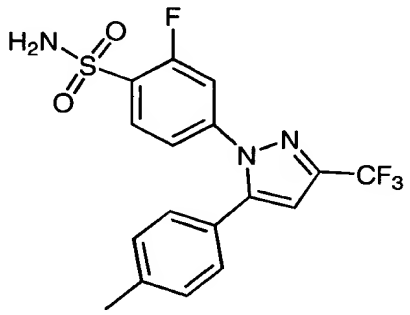
(M+H$^+$, Calcd 206.0400). Anal. Calcd for $C_6H_8FN_3O_2S$: C, 35.13; H, 3.93; N, 20.48; Found: C, 35.18; H, 3.85, N 20.29.



Step 5: Preparation of 4-[5-(3-chloro-4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide

2-Fluoro-4-hydrazinobenzenesulfonamide (0.73 g, 4.0 mmol) was dissolved in ethanol (10 mL) and concentrated hydrochloric acid (0.5 mL) was added. After stirring for 5 minutes at ambient temperature, 1-(3-chloro-4-methylphenyl)-4,4-difluoro-1,3-butanedione (1.08 g, 4 mmol) was added and the reaction was refluxed for 1 hour. The solution was cooled to ambient temperature and water was added until the reaction became cloudy. The reaction mixture was stirred overnight at ambient temperature. The 4-[5-(3-chloro-4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]-2-fluorobenzene-sulfonamide (0.88 g, 2.12 mmol) was isolated as light orange crystals by vacuum filtration directly from the reaction mixture. (0.88 g, (53 % yield): mp 160-161 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.91 (t, 1H, J = 8.1 Hz), 7.42-7.06 (m, 5H), 6.88 (s, 1H), 2.42 (s, 3H). ESHRMS *m/z* 416.0465 (M+H$^+$, Calcd 416.0447). Anal. Calcd for $C_{17}H_{13}ClF_3N_3O_2S$: C, 49.10; H, 3.15; N, 10.11; Found: C, 49.09; H, 2.97, N 9.95.

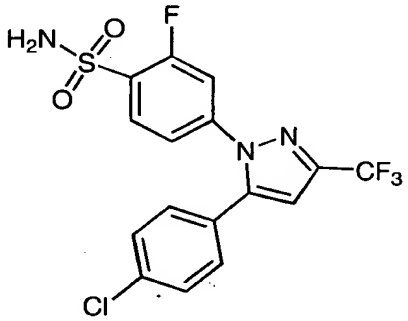
Example 4



4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide

The title compound was obtained by substituting 1-(4-chlorophenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone and ethyl trifluoroacetate for ethyl difluoroacetate using the method described in example 3: mp 126-128 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.80 (m, 2H,), 7.49 (dd, 1H, J = 10.74,1.8 Hz), 7.29 (dd, 1H, J = 8.6,1.88 Hz) (7.16-7.24 m, 5H), 2.29 (s, 3H). ESHRMS m/z 400.0753 (M+H$^+$, Calcd 400.0742).

Example 5

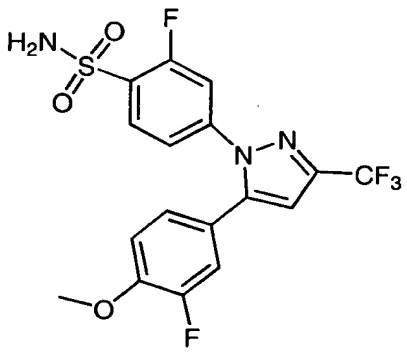


4-[5-(4-Chlorophenyl)- 3-trifluoromethyl-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide

The title compound was obtained by substituting 1-(4-chlorophenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone and ethyl trifluoroacetate for ethyl difluoroacetate using the method described in example 3: mp 140-141 °C. ^{1}H NMR (CD$_3$OD/300 MHz)

7.82 (t, 1H, J = 8.0 Hz), 7.36-7.14 (m, 6H), 6.91 (s, 1H). ESHRMS m/z 420.0224 ($M+H^+$, Calcd 420.0197).

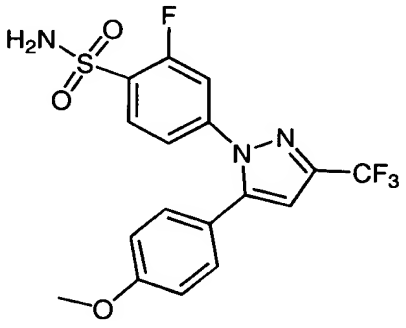
Example 6



4-[5-(3-Fluoro-4-methoxy)-3-trifluoromethyl-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide

The title compound was obtained by substituting 1-(4-fluoro-3-methoxyphenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone and ethyl trifluoroacetate for ethyl difluoroacetate using the method described in example 3: mp 124-126 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.94 (t, 1H, J = 8.3 Hz), 7.29 (dd, 1H, J = 10.5, 2.0 Hz), 7.29 (dd, 1H, J = 8.3, 2.0 Hz), 7.16-7.06 (m, 3H), 6.96 (s, 1H), 3.92 (s, 3H). ESHRMS m/z 434.0598 ($M+H^+$, Calcd 434.0617).

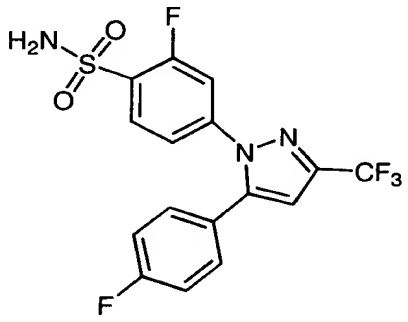
Example 7



2-Fluoro-4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was obtained by substituting 1-(4-methoxyphenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone and ethyl trifluoroacetate for ethyl difluoroacetate using the method described in example 3: mp 130-131 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.88 (t, 1H, J = 8.1 Hz), 7.34 (dd, 1H, J = 10.7, 1.9 Hz), 7.25-7.22 (m, 3H), 6.95 (m, 2H), 6.87 (s, 1H), 3.80 (s, 3H). ESHRMS *m/z* 416.0692 ($M+H^+$, Calcd 416.0680). Anal. Calcd for $C_{17}H_{13}F_4N_3O_3S$: C, 49.16; H, 3.15; N, 10.12; Found: C, 49.20; H, 3.01; N, 9.75.

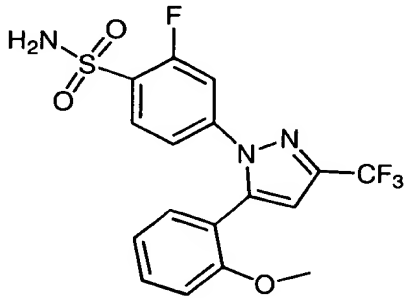
Example 8



2-Fluoro-4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was obtained by substituting 1-(4-fluorophenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone and ethyl trifluoroacetate for ethyl difluoroacetate using the method described in example 3: mp 127-130 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.92 (t, 1H, J = 8.3 Hz). 7.42-7.17 (m, 6H), 7.00 (s, 1H). ESHRMS *m/z* 404.0497 ($M+H^+$, Calcd 404.0492). Anal. Calcd for $C_{16}H_{10}F_5N_3O_2S$: C, 47.65; H, 2.50; N, 10.42; Found: C, 47.43; H, 2.37; N, 10.24.

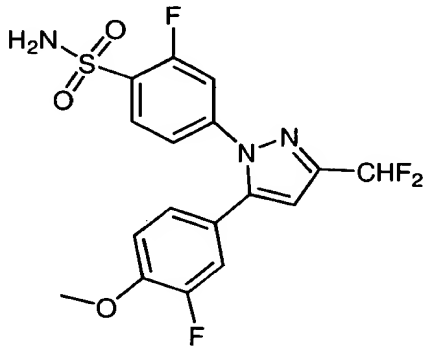
Example 9



2-Fluoro-4-[5-(2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was obtained by substituting 1-(2-methoxyphenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone and ethyl trifluoroacetate for ethyl difluoroacetate using the method described in example 3: mp 159-160 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.61 (t, 1H, J = 8.3 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.34 (d, 1H, J = 7.5), 7.17-7.13 (m, 2H), 7.01 (t, 1H, J = 7.5), 6.91 (d, 1H, J = 8.3), 6.76 (s, 1H), 3.37 (s, 3H). ESHRMS *m/z* 416.0675 ($M+H^+$, Calcd 416.0692). Anal. Calcd for $C_{17}H_{13}F_4N_3O_3S$: C, 49.16; H, 3.15; N, 10.12; Found: C, 49.10; H, 3.12; N, 10.09.

Example 10

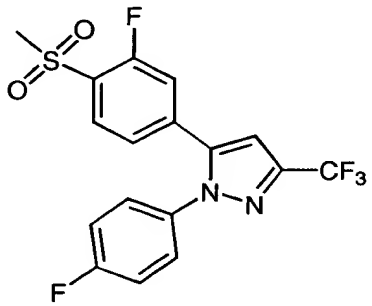


4-[3-(Difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]-2-fluorobenzenesulfonamide

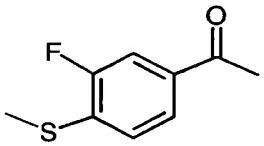
The title compound was obtained by substituting 1-(4-fluoro-3-methoxyphenyl)-ethanone for 1-(3-chloro-4-methylphenyl)-ethanone: mp 167-169 °C. ^{1}H NMR

(CD_3OD/300 MHz) 7.91 (t, 1H, J = 8.1 Hz), 7.39 (dd, 1H, J = 10.9, 2.0 Hz), 7.25 (dd, 1H, J = 8.5, 1.4), 7.17-7.05 (m, 3H), 6.86 (t, 1H, J = 54.5), 6.83 (s, 1H), 3.92 (s, 3H). ESHRMS m/z 416.0721 ($M+H^+$, Calcd 416.0692). Anal. Calcd for $C_{17}H_{13}F_4N_3O_3S$: C, 49.16; H, 3.15; N, 10.12; Found: C, 49.20; H, 3.24; N, 9.95

Example 11



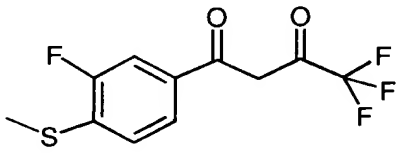
5-[3-Fluoro-4-(methylsulfonyl)phenyl]-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole



Step 1: Preparation of 1-[3-fluoro-4-methylthio)-phenyl]-ethanone

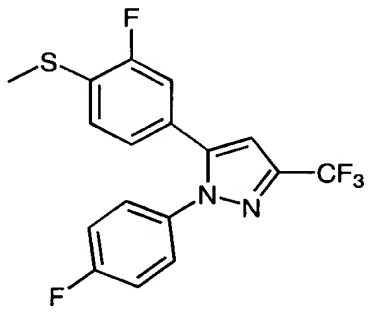
3',4'-Difluoroacetophenone (100 g, 640 mmol) was dissolved in acetonitrile (700 mL). Sodium thiomethoxide was slowly added to the mixture keeping the temperature below 30 °C. The reaction was stirred at ambient temperature overnight. The solids were removed by vacuum filtration and recrystallized from ethyl acetate and hexanes to produce a white crystalline solid, 1-[3-fluoro-4-(methylthio)-phenyl]ethanone (90.5 g, 494 mmol, 77 % yield) mp 72-78 °C. ^1H NMR ($CDCl_3$/300 MHz) 7.74 (dd, 1H, J = 8.3, J = 1.8 Hz). 7.61 (dd, 1H, J = 10.7, J = 1.8), 7.27 (t, 1H, J = 7.8), 2.59 (s, 3H), 2.54 (s, 3H). ESHRMS m/z

185.0412 (M+H$^+$, Calcd 184.0436). Anal. Calcd for C_9H_9FOS: C, 58.67; H, 4.92; Found: C, 58.76; H, 4.85.



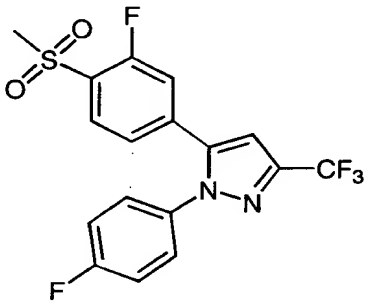
Step 2: Preparation of 4,4,4-trifluoro-1-[3-fluoro-4-(methylthio)phenyl]-1,3-butanedione

1-[3-fluoro-4-(methylthio)phenyl]ethanone (41.50 g, 225 mmol) and ethyl trifluoroacetate was dissolved in diethyl ether (1000 mL). The reaction was stirred at ambient temperature for one hour, aqueous hydrochloric acid was added to adjust the to pH < 1.0. The organics were separated and extracted with water (2 X 250 mL), saturated ammonium chloride (2 X 250 mL) and dried over sodium sulfate. Solvent was removed in *vacuo* and 4,4,4-trifluoro-1-[3-fluoro-4-(methylthio)-phenyl]-1,3-butanedione was recrystallized from ethyl acetate and hexanes (48.00 g, 172 mmol, 76 % yield): mp 66-68 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 15.13 (bs 1H), 7.74 (dd, 1H, J = 8.3, J = 1.8 Hz). 7.61 (dd, 1H, J = 10.7, J = 1.8), 7.28 (t, 1H, J = 7.8), 6.53 (s, 1H), 2.59 (s, 3H). Anal. Calcd for C_9H_9FOS: C, 47.14; H, 2.88; Found: C, 47.50; H, 2.71.



Step 3: Preparation of 5-[3-fluoro-4-(methyl-thio)phenyl]-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole

4,4,4-trifluoro-1-[3-fluoro-4-(methylthio)phenyl]-1,3-butanedione (0.77 g, 2.8 mmol) was dissolved in ethanol (20 mL) and concentrated hydrochloric acid was added to adjust the ph < 1.0. 4-Fluorophenylhydrazine hydrochloride (0.48 g, 2.8 mmol) was added and the mixture was heated to reflux. After one hour, the solvent was removed *in vacuo* and the solid dissolved in ethyl acetate (50 mL). The solution was extracted with water (2 X 50 mL), saturated ammonium chloride (2 X 50 mL), dried over sodium sulfate and solvent was removed *in vacuo*. The resulting yellow oil, 5-[3-fluoro-4-(methylthio)phenyl]-1-(4-fluorophenyl)-3(trifluoro-methyl)-1H-pyrazole was used without further purification. ^{1}H NMR ($CDCl_3$/300 MHz) 7.36-7.27 (m, 2H), 7.22-7.10 (m, 3H), 7.6.98-6.89 (m, 2H), 6.77 (s, 1H), 2.50 (s, 3H). ESHRMS *m/z* 371.0620 ($M+H^+$, Calcd 371.0641).

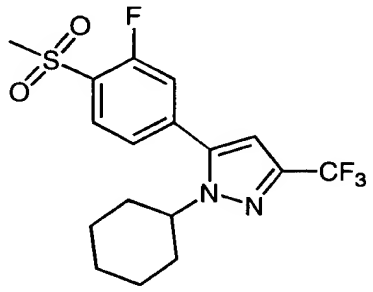


Step 4: Preparation of 5-[3-fluoro-4-(methyl-sulfonyl)phenyl]-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole

5-[3-fluoro-4-(methylthio)phenyl]-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole (1.00 g, 2.75 mmol) and monoperoxyphthalic acid, magnesium salt hexahydrate (2.30 g, 4.69 mmol) were mixed in methylene chloride:methanol (3:1, 20 mL). The mixture was stirred overnight at ambient temperatures. Solids were by vacuum filtration, solvent was removed *in vacuo* and the resulting slurry was dissolved in ethyl acetate (20 mL). The solution was extracted with water (2 X 25 mL), saturated ammonium chloride (2 X 25 mL), dried over sodium sulfate and solvent was removed *in vacuo*. Crystallization from ethyl acetate and hexanes yielded 5-[3-fluoro-4-(methylsulfonyl)phenyl]-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole (0.66 g, 1.64 mmol, 60 % yield): mp 228-229 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.85 (t, 1H, J = 7.8 Hz). 7.59-7.28 (m, 7H), 3.37 (s, 3H). ESHRMS *m/z*

402.0474 (M+H$^+$, Calcd 402.0461). Anal. Calcd for $C_{17}H_{11}F_5O_2S$: C, 50.75; H, 2.76; N, 6.96; Found: C, 50.63; H, 2.57; N, 6.76.

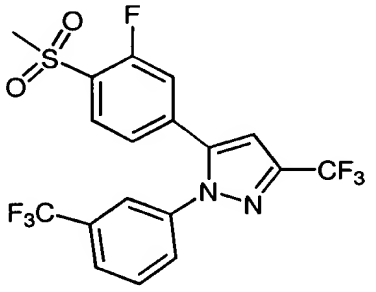
Example 12



1-Cyclohexyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole

The title compound was obtained by substituting cyclohexylhydrazine for 4-fluorophenylhydrazine using the method described in example 11: mp 228-229 °C. ^{1}H NMR (DMSOd_6/300 MHz) 8.02 (t, 1H, J = 7.6 Hz), 7.78 (d, 1H, J = 10.7), 7.62 (d, 1H, J = 8.1), 7.02 (s, 1H), 4.24 (m, 1H), 3.42 (s, 3H), 1.98-1.26 (m, 10H). ESHRMS m/z 390.1022 (M, Calcd 390.1025). Anal. Calcd for $C_{17}H_{18}F_4N_2O_2S$: C, 52.30; H, 4.65; N, 7.18; Found: C, 52.47; H, 4.51; N, 7.11.

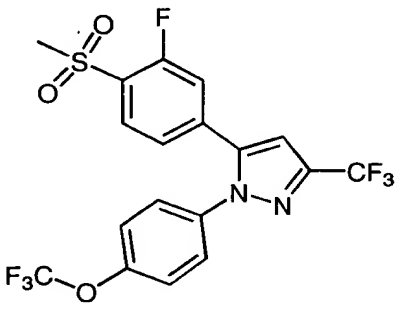
Example 13



5-[3-Fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole

The title compound was obtained by substituting 3-trifluoromethylphenyhydrazine for 4-fluorophenyl-hydrazine using the method described in example 11: 162-168 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.92-7.84 (m, 3H), 7.76 (m, 3H), 7.49 (s, 1H), 7.34 (dd, 1H, J = 8.3, J = 1.4), 3.36 (s, 3H). ESHRMS m/z 452.0418 (M, Calcd 452.0429). Anal. Calcd for $C_{18}H_{11}F_7N_2O_2S$: C, 47.79; H, 2.45; N, 6.19; Found: C, 47.87; H, 2.31; N, 6.12.

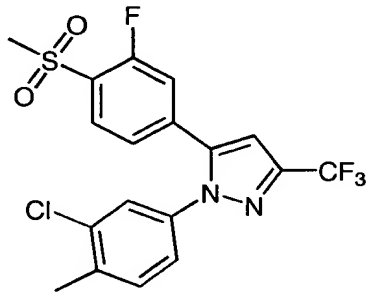
Example 14



5-[3-Fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole

The title compound was obtained by substituting 4-trifluoromethoxyphenyl-hydrazine for 4-fluorophenyl-hydrazine using the method described in example 11: mp 110-112 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.86 (t, 1H, J = 8.0), 7.62-7.52 (m, 5H), 7.47 (s, 1H), 7.34 (dd, 1H, J = 8.0, J = 1.4), 3.37 (s, 3H). ESHRMS m/z 468.0338 (M, Calcd 468.0379). Anal. Calcd for $C_{18}H_{11}F_7N_2O_3S$: C, 46.16; H, 2.37; N, 5.98; Found: C, 46.22; H, 2.49; N, 5.91.

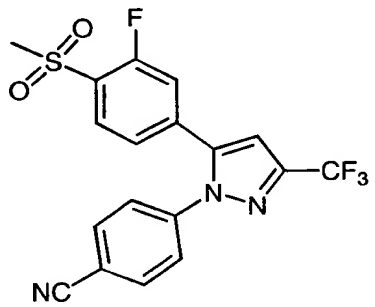
Example 15



1-(3-Chloro-4-methylphenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole

The title compound was obtained by substituting 3-chloro-4-methylphenylhydrazine for 4-fluorophenyl-hydrazine using the method described in example 11: mp 144-145 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.86 (t, 1H, J = 7.7), 7.64-7.60 (m, 2H), 7.48-7.45 (m, 2H), 7.39 (dd, 1H, J = 8.3, J = 2.2), 7.27 (dd, 1H, J = 8.3, J = 2.2), 3.37 (s, 3H), 2.39 (s, 3H). ESHRMS m/z 433.0395 (M+H$^+$, Calcd 433.0401). Anal. Calcd for $C_{18}H_{13}ClF_4N_2O_2S$: C, 49.95; H, 3.03; N, 6.47; Found: C, 49.90; H, 2.84; N, 6.29.

Example 16

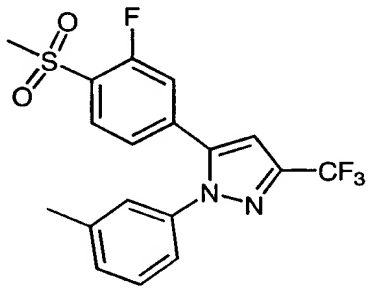


4-[5-[3-Fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile

The title compound was obtained by substituting 4-cyanophenylhydrazine for 4-fluorophenylhydrazine using the method described in example 11: mp 152-153 °C. ^{1}H NMR (DMSOd_6/300 MHz) 8.00 (d, 2H, J = 8.7), 7.87 (t, 1H, J = 7.9), 7.67-7.62 (m, 3H),

7.49 (s, 1H), 7.31 (dd, 1H, J = 8.1, J = 1.4), 3.38 (s, 3H). ESHRMS m/z 427.0830 ($M+NH_4^+$, Calcd 427.0852). Anal. Calcd for $C_{18}H_{11}F_4N_3O_2S$: C, 52.81; H, 2.71; N, 10.26; Found: C, 52.49; H, 2.43; N, 9.87.

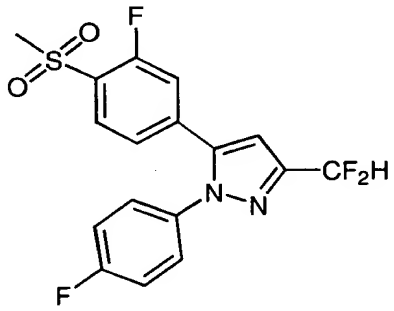
Example 17



5-[3-Fluoro-4-(methylsulfonyl)phenyl]-1-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole

The title compound was obtained by substituting 3-methylphenylhydrazine for 4-fluorophenylhydrazine using the method described in example 11: mp 129-130 °C. ^1H NMR (DMSOd_6/300 MHz) 7.84 (t, 1H, J = 7.9), 7.55 (d, 1H, J = 11.1), 7.44 (s, 1H), 7.38-7.30 (m, 4H), 7.12 (m, 1H), 3.36 (s, 3H), 2.36 (s, 3H). ESHRMS m/z 399.0838 ($M+H^+$, Calcd 399.0790). Anal. Calcd for $C_{18}H_{14}F_4N_3O_2S$: C, 54.27; H, 3.54; N, 7.03; Found: C, 54.11; H, 3.36; N, 7.23.

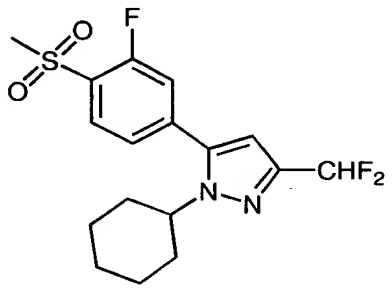
Example 18



3-(Difluoromethyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-1-(4-fluorophenyl)-1H-pyrazole

The title compound was obtained by substituting ethyl difluoroacetate for ethyl trifluoroacetate using the method described in example 11: mp 201-202 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.79 (t, 1H, J = 7.8), 7.65-7.23 (m, 6H), 7.17 (s, 1H), 7.13 (t, 1H, J = 54.2), 3.36 (s, 3H). ESHRMS m/z 385.0643 (M+H$^+$, Calcd 385.0634). Anal. 3.15; N, 7.29; Found: C, 53.01; H, 3.01; N, 7.23.

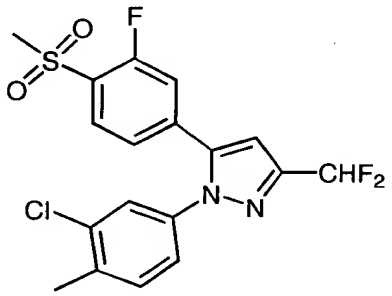
Example 19



1-Cyclohexyl-3-(difluoromethyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-1H-pyrazole

The title compound was obtained by substituting cyclohexylhydrazine for 4-fluorophenylhydrazine and ethyl difluoroacetate for ethyl trifluoroacetate using the method described in example 11: mp 138-139 °C. ^{1}H NMR (DMSOd_6/300 MHz) 8.00 (t, 1H, J = 7.9), 7.74 (d, 1H, J = 10.9), 7.59 (d, 1H, J = 8.1), 7.06 (t, 1H, J = 54.6), 6.79 (s, 1H), 4.20 (m, 1H), 3.42 (s, 3H), 1.96-1.21 (m, 10H). ESHRMS m/z 373.1203 (M+H$^+$, Calcd 373.1198). Anal. Calcd for $C_{17}H_{19}F_3N_2O_2S$: C, 54.83; H, 5.14; N, 7.52; Found: C, 54.84; H, 5.06; N, 7.59.

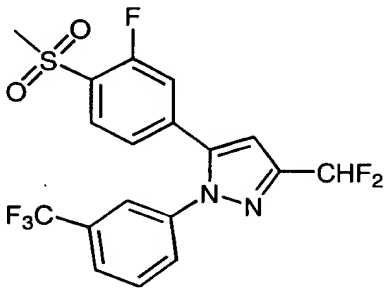
Example 20



1-(3-Chloro-4-methylphenyl)-3-(difluoromethyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-1H-pyrazole

The title compound was obtained by substituting 3-chloro-4-methylphenylhydrazine for 4-fluorophenyl-hydrazine and ethyl difluoroacetate for ethyl trifluoroacetate using the method described in example 11: mp 146-147 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.85 (t, 1H, J = 7.9), 7.62-7.57 (m, 2H), 7.45 (d, 1H, J = 8.3), 7.35 (m, 1H), 7.21 (m, 2H), 7.17 (t, 1H, J = 54.2), 3.37 (s, 3H), 2.39 (s, 3H). ESHRMS m/z 415.0494 (M+H$^+$, Calcd 415.0495). Anal. Calcd for $C_{18}H_{14}ClF_3N_2O_2S$: C, 52.12; H, 3.40; N, 6.75; Found: C, 52.04; H, 3.29; N, 6.75.

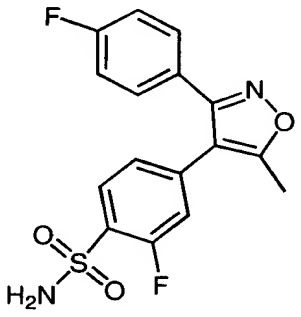
Example 21



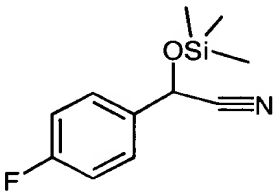
3-(Difluoromethyl)-5-[3-fluoro-4-(methylsulfonyl)-phenyl]-1-[3-(trifluoromethyl)-phenyl]-1H-pyrazole

The title compound was obtained by substituting 3-trifluoromethylphenylhydrazine for 4-fluorophenyl-hydrazine and ethyl difluoroacetate for ethyl trifluoroacetate using the method described in example 11: mp 110-111 °C. ^{1}H NMR (DMSOd_6/300 MHz) 7.88-7.83 (m, 3H), 7.71 (t, 1H, J = 8.1), 7.63-7.59 (m, 2H), 7.33 (dd, 1H, J = 8.3, J = 1.4), 7.25 (s, 1H), 7.21 (t, 1H, J = 54.2), 3.36 (s, 3H). ESHRMS m/z 435.0599 ($M+H^+$, Calcd 435.0602). Anal. Calcd for $C_{18}H_{12}F_6N_2O_2S$: C, 49.77; H, 2.78; N, 6.45; Found: C, 49.77; H, 2.68; N, 6.30.

Example 22



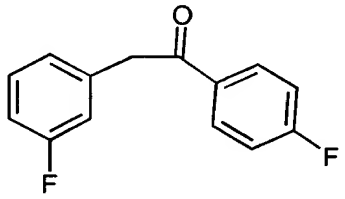
2-Fluoro-4-[3-(4-fluorophenyl)-5-methyl-4-isoxazolyl]-benzenesulfonamide



Step 1: Preparation of 4-fluoro-α-[(trimethylsilyl)-oxy]benzeneacetonitrile

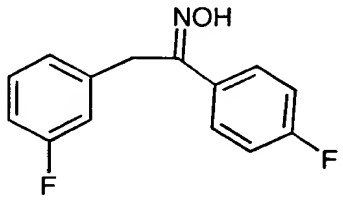
4-Fluorobenzaldehyde (21.0 g, 170 mmol) and zinc iodide (30 mg) were mixed together in methylene chloride (100 mL). The solution was cooled to -70 °C and trimethylsilyl cyanide was slowly added (16.8 g, 170 mmol). The cooling bath was removed and the solution stirred for 1 hour while warming to ambient temperature. The solution was extracted with water (2 X 100 mL), saturated ammonium chloride (2 X 100 mL) and dried

over sodium sulfate. Solvent was removed *in vacuo* to yield 4-fluoro-α-[(trimethylsilyl)oxy]benzene-acetonitrile as a yellow oil (23.0 g, 95.8 mmol, 61 % yield): ^{1}H NMR ($CDCl_3$/300 MHz) 7.46-7.43 (m, 2H), 7.11-7.07 (m, 2H), 5.46 (s, 1H), 0.22 (s, 9H). ESHRMS *m/z* 241.1172 ($M+NH_4^+$, Calcd 241.1172).



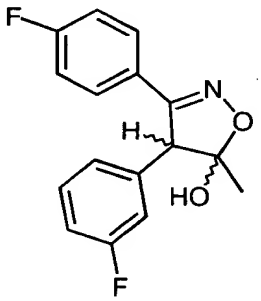
Step 2: Preparation of 2-(3-fluorophenyl)-1-(4-(fluorophenyl)ethanone.

4-Fluoro-α-[(trimethylsilyl)oxy]benzene-acetonitrile (23.0 g, 104 mmol) was cooled to -78 °C in tetrahydrofuran (300 mL). 1.0 M Lithium diisopropylamide in tetrahydrofuran (115 mL, 115 mmol) was added dropwise over 1 hour. The solution was stirred for 1 hour at -78 °C. 3-Fluorobenzyl bromide (19.6 g, 104 mmol) was added as a solution in tetrahydrofuran (100 mL) over 25 minutes. The solution was held at -78 °C for 1 hour then warmed to 0 °C for two hours. Aqueous hydrochloric acid (10 % X 200 mL) was added and the solution and stirred for 24 hours at ambient temperature. The layers were separated and the organic layer was mixed with aqueous 15% sodium hydroxide (100 mL) and stirred for 24 hours at ambient temperature. The organic layer was collected, washed with saturated ammonium chloride(200 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* to afford a yellow oil. 2-(3-fluorophenyl)-1-(4-(fluorophenyl)ethanone (10.15 g, 43.0 mmol) was isolated by preparative silica chromatography followed by crystallization from ethyl acetate and hexanes (42 % yield): mp 47-48 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 8.08-8.03 (m, 2H), 7.33-7.29 (m, 1H), 7.14 (t, 2H, J = 8.7), 7.07-6.96 (m, 3H), 4.28 (s, 2H). ESHRMS *m/z* 233.0791 ($M+H^+$, Calcd 233.0778). Anal. Calcd for $C_{14}H_{11}F_2O$: C, 72.41; H, 4.34; Found: C, 72.32; H, 4.30.



Step 3: Preparation of 2-(3-fluorophenyl)-1(4-fluorophenyl)ethanone oxime

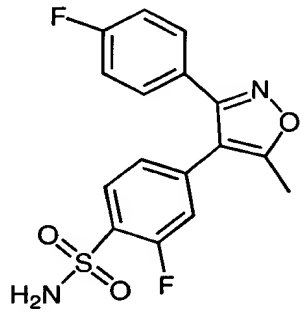
2-(3-fluorophenyl)-1-(4-(fluorophenyl)ethanone (8.82 g, 38 mmol), hydroxylamine hydrochloride (5.55 g, 38 mmol) and ammonium acetate (6.50 g, 38 mmol) was refluxed in ethanol (150 mL) and water (50 mL) for 1 hour. Ethanol was removed *in vacuo* and the aqueous suspension poured into ethyl acetate (200 mL), extracted with water (2 X 200 mL), saturated ammonium chloride (2 X 250 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* and 2-(3-Fluorophenyl)-1(4-fluorophenyl)ethanone oxime (6.19 g, 25.0 mmol) was obtained by crystallization form boiling hexanes (65 % yield): mp 60-67 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.64-7.59 (m, 2H), 7.28-7.23 (m, 1H), 7.10-6.93 (m, 5H), 4.23 (s, 2H). ESHRMS *m/z* 248.0899 ($M+H^+$, Calcd 248.0887). Anal. Calcd for $C_{14}H_{11}F_2NO$: C, 68.01; H, 4.48; N, 5.67; Found: C, 67.86; H, 4.44; N, 5.63.



Step 4: Preparation of 4-(3-fluorophenyl)-3-(4-fluoro-phenyl-4,5-dihydro-5-methyl-5-isoxazolol (mixture of diastereoomers)

2-(3-Fluorophenyl)-1-(4-fluorophenyl)ethanone oxime (7.39 g, 30 mmol) was dissolved in tetrahydrofuran (500 mL) and cooled to -78 °C. 2.5 M n-butyl lithium (50 mL) was added over 1 hour and held at -78 °C for an additional hour. Acetyl imidazole (6.51 g, 60 mmol) was added and the suspension was warmed to ambient temperature. 10 %

Aqueous hydrochloric acid was added to adjust the solution to pH to <1.0. The solution was extracted with water (2 X 250 mL), ammonium chloride (2 X 250 mL) and dried over sodium sulfate. A mixture of 4-(3-Fluorophenyl)-3-(4-fluorophenyl-4,5-dihydro-5-methyl-5-isoxazolol diastereomers was obtained by preparative silica chromatography followed by crystallization from ethyl acetate and hexanes (4.07 g,14.08 mmol, 47 % yield): mp 130-132 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.65-7.60 (m, 2H), 7.39-7.30 (m, 1H), 7.05-6.99 (m, 5H), 4.50 (s, 1H), 3.00 (br s, 1H), 1.33 (s, 3H). ESHRMS *m/z* 290.0993 ($M+H^+$, Calcd 290.0993). Anal. Calcd for $C_{16}H_{13}F_2NO_2$: C, 66.43; H, 4.53; N, 4.84; Found: C, 66.48; H, 4.54; N, 4.76.

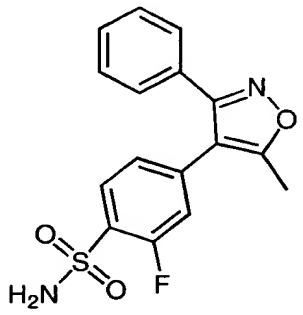


Step 5: Preparation of 2-fluoro-4-[3-(4-fluorophenyl)-5-methyl-4-isoxazolyl]benzenesulfonamide

Chlorosulfonic acid (8.0 mL) was cooled to 0 °C and 4-(3-fluorophenyl)-3-(4-fluorophenyl-4,5-dihydro-5-methyl-5-isoxazolol (0.53 g, 18 mmol) was added. After stirring at 0 °C for 1 hour, the solution was added drop-wise onto ice (200 mL) with vigorous stirring. The solution was extracted with ethyl acetate (2 X 100 mL). The ethyl acetate layers were combined, washed with water (2 X 100 mL), saturated ammonium chloride (2 X 100 mL). Ammonium hydroxide (50 mL) was added to the ethyl acetate solution and the mixture was stirred overnight at ambient temperature. Saturated ammonium chloride was added (50 mL) and the ethyl acetate layer isolated, extracted with saturated ammonium chloride (2 x 100 mL) and dried over sodium sulfate. 2-Fluoro-4-[3-(4-fluorophenyl)-5-methyl-4-isoxazolyl]benzene-sulfonamide (0.10 g, 0.28 mmol) was obtained by preparative silica chromatography followed by crystallization from ethyl acetate

and hexanes (0.10 g, 15 % yield): mp 176-177 °C. ^{1}H NMR (CD_3OD/300 MHz) 6.37 (t, 1H, J = 7.7 Hz), 5.92-5.88 (m, 2H), 5.67-5.60 (m, 4H), 0.98 (s, 3H). ESHRMS *m/z* 351.0598 ($M+H^+$, Calcd 351.0615). Anal. Calcd for $C_{16}H_{12}F_2N_2O_3S$: C, 54.85; H, 3.45; N, 8.00; Found: C, 54.99; H, 3.33; N, 7.82.

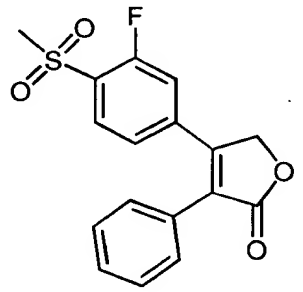
Example 23



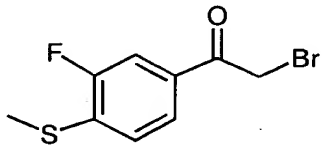
2-Fluoro-4-[3-(4-fluorophenyl)-5-methyl-4-isoxazolyl]-benzenesulfonamide

The title compound was obtained by substituting benzaldehyde for 4-fluorobenzaldehyde using the method described in example 11: mp 180-182 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.86 (m, 1H), 7.38-7.48 (m, 5H), 7.18-7.23 (m, 2H), 6.90 (bs, 1H), 2.52 (s, 3H), ESHRMS *m/z* 333.0727 ($M+H^+$, Calcd 333.0709). Anal. Calcd for $C_{16}H_{13}FN_2O_3S$: C, 57.82; H, 3.94; N, 8.43; Found: C, 57.43; H, 4.00; N, 8.31.

Example 24

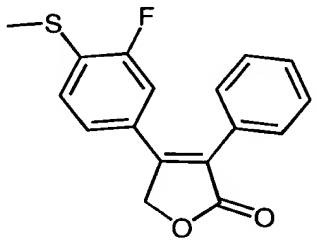


4-[3-Fluoro-4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone



Step 1: Preparation of 2-bromo-1-[3-fluoro-4-(methylthio)phenyl]ethanone

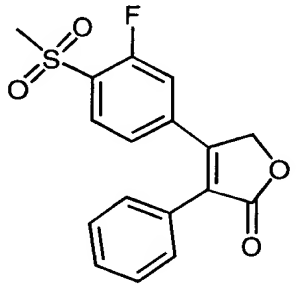
1-[3-Fluoro-4-(methylthio)phenyl]ethanone (10.30 g, 56.0 mmol) was suspended in glacial acetic acid (50 mL) and hydrogen bromide (20 mL, 35% in acetic acid). Bromine (8.95 g, 56 mmol) was added and the reaction was stirred at ambient temperature for 30 minutes. Ethyl acetate (50 mL) was added to the reaction and it was extracted with water (2 X 50 mL), saturated ammonium chloride (2 X 50 mL) and dried over sodium sulfate. Solvent was removed *in vacuo* to yield 2-bromo-1-[3-fluoro-4-(methylthio)-phenyl]ethanone as a yellow solid, (10.45 g, 39.8 mmol, 71 % yield): mp 70-71 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.76 (dd, 1H, J = 8.3, 1.8 Hz), 7.65 (dd, 1H, J = 10.7, 1.8 Hz), 7.29 (t, 1H, J = 7.7 Hz), 4.40 (s, 2H), 2.56 (s, 3H). ESHRMS *m/z* 262.9544 ($M+H^+$, Calcd 262.9542). Anal. Calcd for C_9H_8FBrOS: C, 41.08; H, 3.06; Found: C, 41.00; H, 2.88.



Step 2: Preparation of 4-[3-fluoro-4-(methylthio)-phenyl]-3-phenyl-2(5H)-furanone

Phenylacetic acid (3.61 g, 26.5 mmol) and sodium hydroxide (2.6 g, 50% aqueous) were dissolved in dimethylformamide and stirred vigorously for 15 min. 2-bromo-1-[3-fluoro-4-(methylthio)phenyl]ethanone (5.17 g, 19.6 mmol) was added and the reaction was warmed to 45°C for one hour. Ethyl acetate (50 mL) was added to the reaction and the organics were extracted with 10% aqueous hydrochloric acid (2 X 50 mL), water (2 X 50 mL), saturated ammonium chloride (2 X 50 mL) and dried over sodium sulfate. Solvent was removed *in vacuo* to yield a yellow solid. The solid was dissolved in methylene chloride and concentrated sulfuric acid (1 mL) was added. After 15 min, the solution was

extracted with water (2 X 50 mL), saturated ammonium chloride (2 X 50 mL) and dried over sodium sulfate. The solvent was removed *in vauo* and 4-[3-fluoro-4-(methylthio)phenyl]-3-phenyl-2(5H)-furanone (1.85 g,6.16 mmol) was obtained by crystallization from ethyl acetate and (31 % yield): mp 159-160 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.46-7.44 (m, 5H), 7.20-7.09 (m, 2H), 7.00 (dd, 1H, J = 11.1, 1.8 Hz), 5.17 (s, 2H), 2.50 (s, 3H). ESHRMS *m/z* 301.0680 ($M+H^+$, Calcd 301.0699). Anal. Calcd for $C_{17}H_{13}FO_2S$: C, 67.98; H, 4.36; Found: C, 67.55; H, 4.10.



Step 3: Preparation of 4-[3-fluoro-4-(methylsulfonyl)-phenyl]-3-phenyl-2(5H)-furanone

4-[3-Fluoro-4-(methylthio)phenyl]-3-phenyl-2(5H)-furanone (1.80 g, 6.00 mmol) and monoperoxyphthalic acid magnesium salt hexahydrate (3.70 g, 6.00 mmol) were mixed in methylene chloride: methanol (3:1, 40 mL). The mixture was stirred overnight at ambient temperatures. Solids were removed by vacuum filtration and discarded, solvent was removed *in vacuo* and the resulting slurry was dissolved in ethyl acetate (20 mL). The solution was extracted with water (2 X 25 mL), saturated ammonium chloride (2 X 25 mL), dried over sodium sulfate and solvent was removed *in vacuo*. Crystallization from ethyl acetate and hexanes yielded 4-[3-fluoro-4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone (0.63 g,1.89 mmol, 32 % yield): mp 161-162 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.98 (t, 1H, J = 8.5 Hz), 7.47-7.40 (m, 5H), 7.30 (dd, 1H, J = 8.3, 1.6), 7.21 (dd, 1H, J = 10.5, 1.4), 5.20 (s, 2H), 3.26 (s, 1H). ESHRMS *m/z* 333.0606 ($M+H^+$, Calcd 333.0597). Anal. Calcd for $C_{17}H_{13}FO_4S$: C, 61.44; H, 3.94; Found: C, 61.65; H, 3.93.

BIOLOGICAL EVALUATION

Evaluation of COX-1 and COX-2 activity in vitro

The compounds of this invention exhibited inhibition in vitro of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

A. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [J. Biochem., 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (Baculovirus Expression Vectors: A Laboratory Manual (1992)). Recombinant baculoviruses were isolated by transfecting 4 μg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/mL) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 x 10^6/mL) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

B. Assay for COX-1 and COX-2 activity

COX activity was assayed as PGE_2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the

appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 μM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37 °C/room temperature by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table I.

TABLE I

Example	Human COX-2 IC_{50} (μM)	Human COX-1 IC_{50} (μM)
1	0.011	37.9
2	0.051	>100
3	0.005	16.3
4	0.019	40.5
5	0.005	45.9
6	0.025	45.6
7	0.005	7.72
8	0.020	56.8
9	0.250	>100
10	0.110	>100
11	0.150	>100
12	0.180	>100
13	0.180	>100
14	0.062	>100
15	0.016	>100
16	0.250	>100
17	1.05	>100
18	0.320	>100
19	0.700	>100
20	0.036	>100
21	0.550	>100
22	0.015	>100
23	0.020	>100
24	15.9	>100

C. Fast assay for COX-1 and COX-2 activity

COX activity was assayed as PGE_2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 μM phenol, 1 μM heme, 300 μM epinephrine) with the addition of 20 μl of 100 μM arachidonic acid (10 μM). Compounds were pre-incubated with the enzyme for 10 minutes at 25 ^{o}C prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after two minutes at 37 ^{o}C/room temperature by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II

Example	Human COX-2 IC_{50} (μM)	Human COX-1 IC_{50} (μM)
1	0.013	29.4
2	0.043	>100
3	0.004	26.9
4	0.006	20.3
5	0.004	19.9
6	0.018	>100
7	0.004	5.25
8	0.021	41.5
9	0.180	>100
10	na	na
11	0.130	22.6
12	0.140	>100
13	0.150	>100
14	0.064	>100
15	0.015	2.36
16	0.870	>100
17	0.027	4.36
18	0.310	>100
19	0.340	>100
20	0.053	>100

21	0.290	>100
22	0.005	>100
23	0.019	>100
24	3.73	>100

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, et al., (Proc. Soc. Exp. Biol. Med., 111, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, Laboratory Models for Testing NSAIDs, in Non-steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed. 1985)).

Rat Carrageenan-induced Analgesia Test

The rat carrageenan analgesia test is performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, **32**, 77 (1988)). Male Sprague-Dawley rats are treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turns off the lamp and timer when light is interrupted by paw withdrawal. The time until the rat withdraws its foot is then measured. The withdrawal latency in

seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal is determined.

As various changes could be made in the above methods and apparatus without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense. All documents mentioned in this application are expressly incorporated by reference as if fully set forth at length.

All mentioned references are incorporated by reference as if here written. When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.